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Cytokines - major molecular messengers orchestrate between inflammation and cancer

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ABSTRACT

Inflammation is the defensive mechanism against physical or chemical or thermal or infectious agents. Acute inflammation is a protective mechanism against any noxious stimuli by various mediators such as cytokines, chemokines, enzymes, growth factors by inflammatory cells. If the inflammation is aggrevated chronically, smouldering inflammation results in release of inflammatory mediators such as cytokines, chemokines, growth factors, proteolytic enzymes, from innate and adaptive immune cells results in tumor initiation, tumor promotion and tumor progression. Cytokines are intercellular molecular messengers between immune cells and cancer cells, synthesized from immune cells and stromal cells activate transcription factors bring about tumor progression by cell proliferation, cell survival, angiogenesis, genomic instability, epithelial to mesenchymal transition, invasion and metastasis. This article briefs about the role of IL-1, TNF-α, IL-6, IL-8, IL-10, TGF-β, and IL-17 cytokines in progression of cancer.

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Keywords: Interleukin-8, interleukin-10, TNF-α, TGF-β, STAT-3, NF-κB

Introduction

Most of all solid tumors have inflammatory cells and their mediators in their tumor microenvironment. External environmental factors play a very important role in cancer. Inflammatory mediators in tumor microenvironment promote tumor initiation, promotion and progression. Chronic inflammatory conditions induced tumor progression are ulcerative colitis and Crohn's disease induced colorectal cancer, hepatitis B and C induced hepatocellular cancer, chronic periodontitis induced oral squamous cell carcinoma, oral potentially premalignant conditions (Lichen planus and oral submucous fibrosis) induced oral squamous cell carcinoma, prostatitis induced prostate cancer, hPV induced oropharyngeal carcinoma and cervical cancer, smoking induced lung carcinoma, gastric cancer associated with chronic gastritis (H. *Pylori*), esophageal cancer associated with Barret's esophagitis, gall bladder carcinoma associated with chronic cholecystitis, endometrial carcinoma associated with endometriosis. Chronic inflammation is considered as a seventh hallmark of cancer.

Interleukins are intercellular messenger molecules discovered in the 1970. Cytokines develop a specific immune response to a target antigen by

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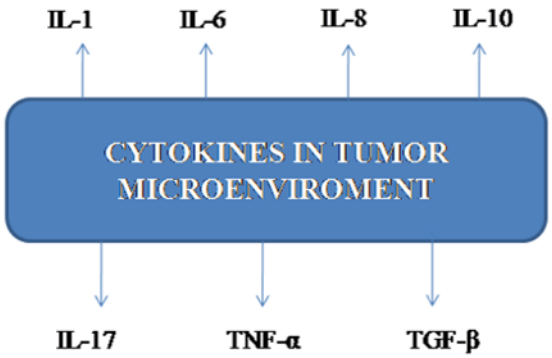

Figure 1. Cytokines in inflammatory tumor microenvironment are IL-1, TNF-α , TGf-β , IL-6, IL-8, IL-10 and IL-17.

communicating cells of the immune system [1, 2].

Interleukins are secreted by immune cells such as CD4 T helper cells, monocytes, macrophages and endothelial cells. They attach to a surface specific cell receptor, triggers a cascade of events in the target cell alters cell behavior. Interleukins also has immunomodulatory functions through maturation, migration, differentiation and adhesion of the cells of the immune system [3].

In inflammatory microenvironment recruit immune cells produce cytokines, chemokines, growth factors, activate transcription factors such as NF-κB, STAT-3, recruit chemokines, cytokines, prostaglandins activate transcription factors such as NF-κB, STAT-3, from cancer cells involved in cell proliferation, cell survival, angiogenesis, genomic instability, epithelial to mesenchymal transition, invasion and metastasis. Cytokines are involved in pro-inflammatory or anti-inflammatory action depends on cytokine concentrations, expression of cytokine receptor content, state of activation of surrounding cells. They stimulate stromal and immune effector cells at tumor site and enhances cytotoxic effects of immune cells to tumor cells. Recent studies has shown that interleukins have major role in tumor driven molecular mechanism. Tumor as it progress and evolve, they evade by the immune system recognition by recruiting inflammatory cells secretes various cytokines in tumor microenvironment, which in turn stimulates biomarkers such as transcriptional factors involved in induction of EMT (Epithelial to mesenchymal transition) markers, anti-apoptotic molecules and cancer stem cells. Cytokines such as TNF-α, TGF-β, IL-1, IL-8, IL-10, IL-6and IL-17 creates a conducive inflammatory environment of tumor driven immunosuppression, tumor growth and metastasis [4-6] (Figure 1).

Cytokines in tumor microenvironment

Cytokines secreted by immune cells involved in tumor progression by promoting cell proliferation, angiogenesis, genomic instability, cell survival, immunosuppression, invasion and metastasis (Figure 2).

IL-1 is a pleotropic cytokine are of two subtypes IL-1α and IL-1β with encoding two separate genes have an identical biological activity through same receptor complex produce by variety of cells such as monocytes, macrophages, keratinocytes and endothelial cells activate T cells and B lymphocytes.

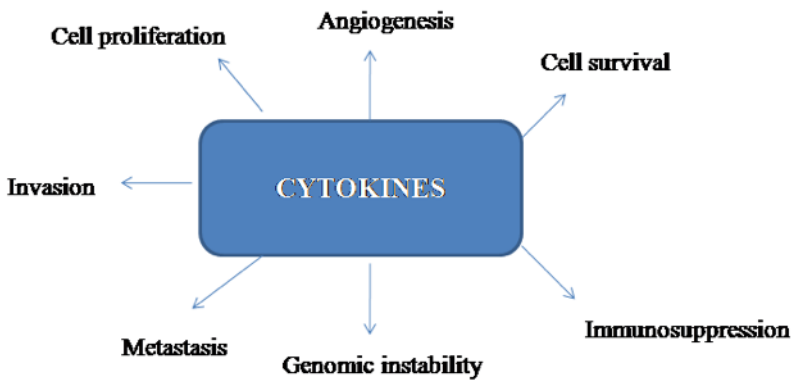

Figure 2. Cytokines secreted by immune cells involved in tumor progression by promoting cell proliferation, angiogenesis, genomic instability, cell survival, immunosuppression, invasion and metastasis.

IL-1α is localized in cell membrane, cytosol and regulates intracellular microenvironment binds to IL-1R1 expressed in most cell types and responsible for IL-1 signal transduction. IL-1β is located extracellularly binds to IL-R11 present on neutrophils, monocytes, B lymphocytes and decrease signal transduction of IL-1 produced by human cancer cells. IL-1 β activates NF-κB a key transcriptional factor, which inturn induce expression of IL-8, TNF-α, VEGF, IL-6 and TGF-β promotes tumor progression in various human cancers. This protein acts through induction of prometastatic genes such as MMPs, angiogenic proteins and growth factors such as VEGF, IL-8, IL-6, TNF-α and TGF-β, further activates MAPK-AP-1, NF-κB and P13/AKT signaling pathway, promote tumor growth and metastasis in several human tumors such as melanoma, head and neck squamous cell carcinoma, colon, lung and breast cancer [7-9].

IL-6 is a potent inflammatory cytokine, it is a key growth promoting and anti-apoptotic factor, produced mainly by macrophages, dendritic cells, and B lymphocytes as well as fibroblasts, epithelial cells and endothelial cells. IL-6 stimulates target cells via binding to IL-6R activates transcriptional factor STAT3 acts on malignant cells. It also increases VEGF expression involved in angiogenesis, cell proliferation, cell survival, invasion and epithelial to mesenchymal transition in head and neck cancer cells and increasing their metastatic potential in human cancers such as oral squamous cell carcinoma, gastric cancer and multiple myeloma [10-12].

IL-8 is a cytokine produced by macrophages, epithelial cells also known as neutrophil chemotactic factor induced by variety of stimuli are LPS, cytokines such as IL-1, TNF- α and bacterial or viral products. Transcriptional factor such as NF-κB is an essential for IL-8 expression was dependent on hypoxia, cellular stress, nitric oxide (NO), acidosis, and a potent promoter of angiogenesis, aggressive growth and metastasis in many human cancers such as head and neck cancer, breast, cervical, prostate, colon, gastric, lung, melanoma, brain, mesothelioma, ovarian cancer and hematological malignancies such as AML, CLL and Hodgkin's lymphoma [13-16].

IL-10 is secreted by alternatively activated T cells phenotype (Th2 cells) acts on macrophages, T cells, B cells, monocytes, dendritic cells, granulocytes, and mast cells inhibits antigenic cell presentation, cell maturation and differentiation allowing evasion of immune surveillance by tumor cells and cytokine production acts as immunosuppressive and anti-inflammatory role. It inhibits the activation of transcription factor NF-κB and stimulating STAT3 activation, there by inhibiting pro-inflammatory cytokine production such as TNF-α, IL-6, and IL-12. It has also shown to modulate apoptosis, angiogenesis suppression and pro-tumorigenic effect in cancers such as in B cell lymphoma prognosis is poor, promotes head and neck cancer and Burkitt's lymphoma [17-20].

TNF-α involved in chronic inflammatory diseases induced carcinogenesis by promoting angiogenesis, invasion, tumor progression have been demonstrated. It is produced by tumor and stromal cells or inflammatory cells such as macrophages, T cells, B cells and endothelial cells in tumor microenvironment, promotes cancer cell survival by induction of NF-κB encoding genes dependent anti-apoptotic molecules such as BCL-2, BCL-XL, surviving, CFLIP, and TRAF1/2. TNF-α dependent tumor promotion based on direct oncogene activation and generation of genotoxic molecules such as reactive oxygen species (ROS) and reactive nitrogen species (RNS), induce DNA damage and mutations, facilitating tumorigenesis. Other actions of TNF-α include immunosuppression of T cell response, cytotoxic activity of macrophages, and promotion of angiogenesis by its ability to cause differentiation of myeloid progenitor cells in to endothelial cells in tumor microenvironment. Pro-tumoral activity of TNF-α mediated via TNFR1 receptor found on tumor and stromal cells, whereas, TNFR2 receptor found on leucocyte infiltrate, stimulating autocrine growth, acting via cross talk between EtK-VEGFR2. TNF-· also promotes metastasis by inducing epithelial-mesenchymal transition (EMT) and found elevated in plasma of patients with advanced cancer, which helps in prognostic purpose in many cancers such as head and neck cancer, lung carcinoma, skin cancer, ovarian cancer [21-23].

TGF-β is a pleotropic immunosuppressive and anti-inflammatory cytokine produced by tumor cells, stromal cells, including cancer associated fibroblasts and immune cells such as T cells and macrophages in tumor microenvironment. Paradoxical complex role of TGF-β in tumor is documented, in an early stage of cancer, it acts as a tumor suppressor, promoting apoptosis and inhibiting cell cycle progression through P21 up-regulation and MYC down-regulation. In later stages of tumor it enhances immunosuppression by converting effector T cells in to regulatory T cells (T

Table 1. Role of cytokines in tumor progression

Cytokines	Source	Action
IL-1	Monocytes	Angiogenesis
	Macrophages	Immune suppression
	Endothelial cells	Tumor progression
	Neutrophils	
TNF-α	Macrophages	Genetic mutation
	Mast cells	Immune suppression
	T and B cells	Angiogenesis
		Invasion and metastasis
IL-6	Dendritic cell	Cell proliferation
	Macrophages	Cell survival
	B-Iymphocytes	
IL-8	Macrophages	Angiogenesis
IL-10	Mast cell	Immune suppression
	Macrophages	Cell survival
	Monocytes	Cell proliferation
	Dendritic cells	
	Granulocytes	
	T and B cells	
TGF-β	T cells	Epithelial mesenchymal
	Carcinoma associated fibroblasts	Transition (EMT)
	Tumor cells	Immune suppression
	Macrophages	
IL-17	Macrophages	Immune suppression
	Mastr cells	Chronic inflammation
		Angiogenesis
		Tumor progression

reg), tumor invasion and metastasis by inducing epithelial mesenchymal transition (EMT) through Smad, Slug and snail transcription factors. TGF-β receptor mutation or deletion leading to poor prognosis in cancers such as oral squamous cell carcinoma, colorectal, gastric, prostate, non-small cell lung, breast, bladder cancer [24-26].

IL-17 is a pleiotropic, procarcinogenic cytokine is a subtype of CD4 T cells produced by CD4 Th17 cells, expressed by tumor associated macrophages involved in tumor progression, induced by IL-23 pro-inflammatory cytokine in tumor microenvironment. It is involved in promoting inflammation and angiogenesis by production of TNF-α, IL-6 and IL-1β induced activation of STAT3 and NF-KB transcription factors, promotes tumor progression in human carcinomas such as oral squamous cell carcinoma, non-Hodgkin's lymphoma, breast, colon, gastric, hepatocellular, melanoma, ovarian, pancreatic, prostate, renal cell, and small cell lung cancer [27-30] (Table1).

Conclusion and Future Perspective

Chronic inflammation promotes tumor initiation and progression by releasing inflammatory mediators such as cytokines (IL-1,IL-6, IL-10, TGF-β, IL-8 and TNF-α) from innate and adaptive immune cells. Cytokines are chemical mediators, which acts as a messenger between immune, cancer and stromal cells to bring about cell proliferation, cell survival, immunosuppression, genomic instability, angiogenesis, invasion and metastasis by activating transcriptional factors such as (NF-κB, STAT3, HIF-1α). It acts as a biological markers, therapeutic target and prognostic markers in cancers. So, thorough understanding of cytokines, their role, and interaction with cancer cells needed for future perpective. Understanding of interaction of cytokines with immune cells, stroma and cancer cells in tumor microenvironment, their signaling pathway, role in tumor progression, helps in future diagnostic, therapeutic and prognostic purpose.

Conflict of interest

The author disclosed no conflict of interest during the preparation or publication of this manuscript.

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Abbreviations

HGF = hepatic growth factor, VEGF = vascular endothelial growth factor, MMP-9 = matrix metaloproteinases-9, NO = nitric oxide, ROS = reactive oxygen species, PDGF = platelet derived growth factor, EGF = epidermal growth factor, FGF = fibroblast growth factor, TNF-· = tumor necrosis factor-alfa, IFN-β = interferon-beta, IL-10 = interleukin 10, TGF-β = transforming growth factor-beta, PGE2 = prostaglandin E2, IDO = indoleamine 2,3-dioxygenase, IL-2 = interleukin-2, IL-4 = interleukin-4, IL-6 = interleukin-6, IFN-γ = interferon-gamma, COX2 = cyclo-oxygenase 2, NF-KB = Neuclear factor kappa B, IL-17 = interleukin-17, CD4+Th17 = CD4+T helper lymphocyte 17, STAT3 = signal transducer and activator of transcription 3, bFGF = basic fibroblast growth factor, MMPS = matrix metallo proteinases, HIF-1· = hypoxia-inducible factor-alfa. Treg cell = T regulatory cell, TAM = tumor associated macrophages, AP-1 = activator protein 1, EMT = epithelial mesenchymal transition, MAPK = mitogen-activated protein kinase, P13k = phosphatidylinositol 3-kinase, IL-8 = interleukin-8, LPS = lipopolysaccharide, Th2 cell = T helper 2 cell, IL-1 = interleukin-1

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Original Article

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Determination of minimum serum concentration to develop scaffold free micro-tissue

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ABSTRACT

Objective. Formation of three-dimensional (3D) micro-tissues without scaffolds are widely used not only to define *in vivo* tissue formation mechanisms but also the development of different tissue-specific drugs. However, depending on high serum and growth factor concentrations, it would be hard to identify major effective biological cues on micro-tissue formation. The aim of the study is to determine the effect of different serum concentrations on Human Umbilicial Vein Endothelial Cells (HUVECs) micro-tissue formation. ***Methods.*** Micro-tissue of HUVEC line was formed by using 3D petri dish technique with medium containing 0%, 1%, 5% and 10% fetal bovine serum (FBS). On the 7th day after micro-tissue formation, live/dead cells analysis was conducted. Micrograph taken on days 1, 3, 5 and 7th of micro-tissue formation were determined by image analysis with ImageJ. ***Results.*** Sizes of micro-tissue formed with 0% FBS on day 1 and 3 determined as 277 ± 12 µm and 279 ± 20 µm, respectively; however, especially on day 7 micro-tissue size significantly decreased to 229 ± 6 µm. When live/dead analysis results were examined, high cell viability was observed in 5% and 10% FBS concentration. Although micro-tissue like structures were observed in 0% and 1% FBS concentrations dead cell ratio considerably increased compared to 5% and 10% FBS concentration. ***Conclusions.*** It has been determined that 0% and 1% serum are appropriate for determining the efficacy of biomimetic peptides and different extracellular matrix proteins on micro-tissue formation parameters of HUVEC. High cell viability in micro-tissues was observed with 5% and 10% serum concentrations.

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Keywords: micro-tissue, three-dimensional cell culture, serum concentration

Introduction

Cell based *in vitro* evaluation techniques including drug diffusion, drug toxicity and release kinetics of controlled drug delivery constructs are substantial to identify the physiological processes and treatments of disease. Moreover, three-dimensional (3D) tissue formation characteristics of mainly vascularized tissues requires extensive exploration to investigate the characteristics of such tissue formation in micro scale [1]. The common issue in between understanding the tissue formation characteristics for regenerative

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medicine and drug evaluations is the necessity of a designed structure that ideally mimics *in vivo* tissue constructs. Since all tissue formations occurs in 3D where cell-cell signaling, and cell-extracellular matrix interactions govern the tissue formation, it would be hard to estimate tissue formation characteristics and drug toxicity evaluations by two-dimensional (2D) culture methods. Therefore, development of 3D scaffold free human micro-tissues is a vital importance for pharmaceutical evaluations and tissue engineering [2, 3].

Regenerative medicine mostly relies on developing engineered 3D tissue constructs on pre-designed scaffolds. However, due to the lack of essential biological cues in pre-designed scaffolds, tissue regeneration is negatively affected. To overcome this limitation, scaffold-free approach in which 3D micro-tissue is developed through cells own extracellular matrix has been widely used to ideally mimic *in vivo* tissue formation [4]. Comparing the conventional 3D scaffolding approach, self-assembly of cells into micro-tissue structures allows interactions among cells and extracellular matrix secretion without requirement of additional matrix material [5]. Scaffold-free approach can effectively overcome the limitations caused by scaffolding materials such as adequately mimicking the natural extracellular matrix, limited cell-cell communication, non-matching remodeling and degradation profile [6, 7].

Human Umbilical Vein Endothelial Cells (HUVECs) are considered promising cell sources for their capacity to differentiate into endothelial cells and high proliferation rate. Vascularization is a key process in engineering of 3D thick micro-tissues structures to prevent cell death due to the limited diffusion capacity of oxygen and nutrients [8]. For instance, Dissanayaka et al. [9] successfully developed vascularized dental pulp scaffold-free 3D micro-tissue that ideally mimics the cellular microenvironment of dental pulp cells.
Micro-tissue formation in micro levels generally requires rich protein and growth factor concentration. Serum as media supplements is the major source of proteins and growth factors. The most common type of serum used in scaffold-free micro-tissue formation is fetal bovine serum (FBS) [10, 11]. However, the media that contains high serum and growth factor concentrations, it would be hard to identify different parameters such as proteins, cell-cell interaction and biomimetic peptides that are functional on micro-tissue formation. In addition, in drug discovery studies serum-drug reaction might occur which inhibits exploring the effect of discovered drug molecules [12, 13]. Therefore, the aim of the study is to determine the effect of FBS concentrations on scaffold-free micro-tissue formation by using HUVECs. The effect of FBS concentration on scaffold-free micro-tissue formation was investigated by measuring the sizes of micro-tissues and live/dead cell assay. Determining the minimal FBS content that allows initial micro-tissue formation could potentially be used for vascular tissue engineering and drug discovery studies.

Methods

Cell Culture

HUVEC line passage five was taken from Ege University Bioengineering Department Tissue Engineering and Animal Cell Culture Laboratory and used in all experiments. HUVEC were cultured with EBM (Endothelium Cell Basal Medium, Lonza, Allendale. NJ, USA) medium which includes 10% FBS (Sigma Aldrich, St. Louis, Missouri, USA), 1% penicilin-streptavidin, and 1% L-Glutamine (Genaxxon BioScience, Ulm, Germany). The media was changed every 2 days and cells were passaged when reached 80% confluency. Six micro-tissues were formed for each of 0%, 1%, 5% and 10% FBS experimental groups. Micrographs of six different micro-tissues were captured at day 1, 3, 5, and 7 by fluorescent microscopy. (CX41, Olympus, Germany) to analyze the average diameters of micro-tissues by using the ImageJ software (NIH, Bethesda, MD, USA http:// www.rsb.info.nih.gov/ij).

Fabrication of 3D Cell Culture

Micro-tissues by using HUVECs were fabricated with 3D petri dish in 24 well plate (Sigma, MicroTissues, Inc, USA) (Figure 1A-D). 330 µl agarose was added into autoclaved petri dishes by using aseptic technique in sterile cabin. Gelled agarose was cautiously put into 24 well plate. The agarose was incubated minimum 30 min with 500µl medium. After incubation, medium removed and HUVECs were added 12.000 cells in 75 µl. After one hour once the cells precipitated due to gravity into the micro-wells, EBM was added with 500 µl in different serum concentration.

Live and Dead Analysis

Double Staining Kit (Dojindo, Molecular Technologies, Inc, Japan) was used to show cell viability in micro-tissues. The medium was carefully

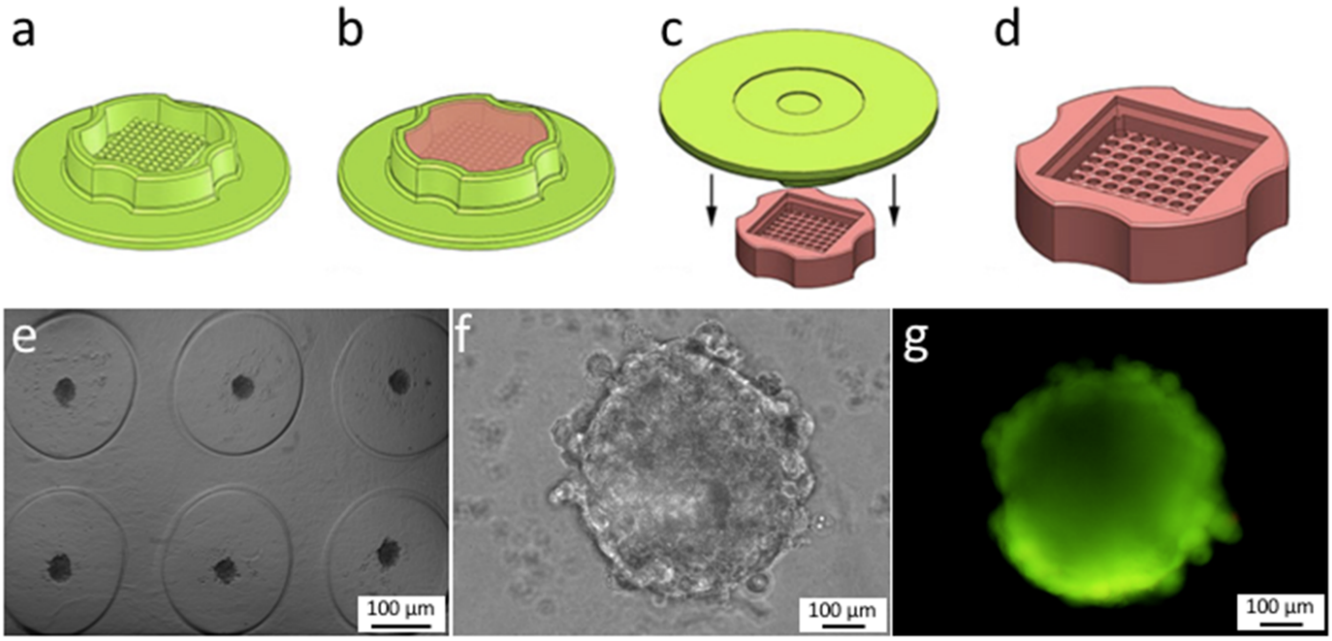

Figure 1. Fabrication of scaffold free micro-tissue. (a) 3D Micro-tissue fabrication plastic mould, (b) Mould filled with agarose, (c) 3D Petri dish of agarose gel separated from the mould, (d) Final 3D Petri dish, (e) Low (3×) and (f) high (20×) magnification of developed micro-tissues with 10% FBS containing media, (g) A representative micrograph of the LIVE/DEAD assay of micro-tissues with 10% FBS containing media. FBS = fetal bovine serum.

removed from the agarose and then washed 3 times with PBS. Stock solution was prepared by using 1 mmol/L solution A-green (Calcein-AM/DMSO) and 1.5 mmol/L solution B-red (PI (Propidium iodide) /purified water) in sterile PBS. After incubation for 15 min at 37°C in dark environment, the solution was removed. The micro-tissues were washed 5 times with PBS to prevent unspecific staining. The micrographs were taken by fluoresent microscope. Green dye represents living cells and red dye symbolizes dead cells. Both live and dead cell images were taken separately and then merged with CellSense Entry software (Olympus, Germany). Live&Dead assay was performed on three micro-tissues for each experimental group. Fluorescence pixel intensities for each group were measured by Image J and presented as mean fluorescence pixel intensity ± Standard Error.

Statistical Analysis

All data were expressed as mean ± standard error and were statistically analysed by one-way ANOVA (SPSS 12.0, SPSS GmbH, Germany) and the Student-Newman-Keuls method as a post hoc test. Significant differences between groups were determined at p values at least less than 0.05.

Results

The micro-tissues with different FBS concentration were developed by using 3D petri dish technique as explained in methods section (Figures 1A, 1B, 1C and 1D). The low and high magnifications micrographs of 3D micro-tissues developed after 7 days of culture with 10% FBS included media were presented in Figures 1E and 1F. As depicted from the figure, micro-tissue formation successfully occurred with the initial cell concentration of 12,000 cells in 75 µl. It was also observed that cell viability is quite high in micro-tissues formed with 10% FBS included media (Figure 1G).

Early micro-tissue formation response of the monodispersed cells in 0%, 1%, 5%, and 10% FBS concentrations are presented in Figures 2A, 2B, 2C, and 2D, respectively. The average diameters of micro-tissue like constructs for 0%, 1%, 5%, and 10% FBS at day 1 are 277.1 ± 12.4 µm, 287.6 ± 16.1 µm, 294.7 ± 7.9 µm, and 302.2 ± 2.2 µm, respectively. There was no statistically significant difference among the different FBS containing groups. Micro-tissue micrographs at day 7 for 0%, 1%, 5%, and 10% FBS concentrations are presented in Figures 3A, 3B, 3C, and 3D, respectively. The average diameters of micro-tissue like constructs for 0%, 1%, 5%, and 10% FBS

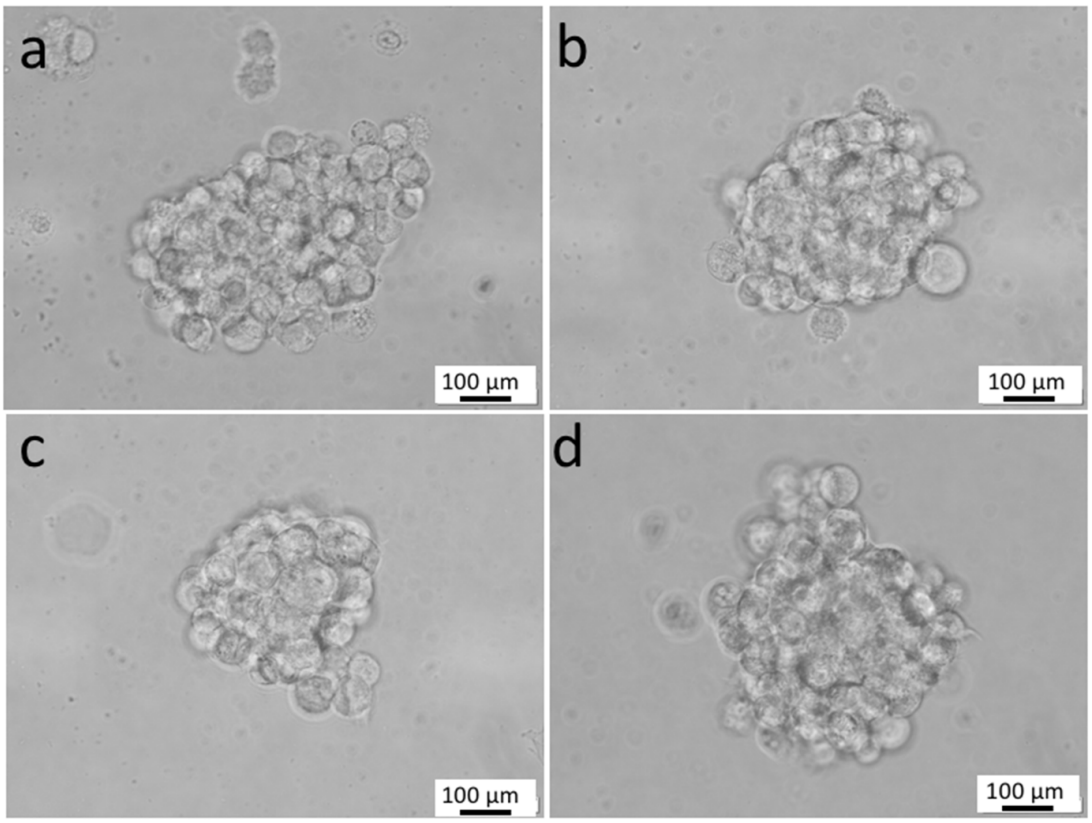

Figure 2. Micrographs of developed micro-tissues with 0% (a), 1% (b), 5% (c), and 10% (d) FBS containing media at day 1. FBS = fetal bovine serum. Scale bar represents 100 µm size.

at day 1, 3, 5, and 7 are given in Figure 4. The average diameter at day 7 for 0%, 1%, 5%, and 10% FBS micro-tissue groups were measured as 229.4 ± 12.4 µm, 310.9 ± 16.1 µm, 332.4 ± 7.9 µm, 368.5 ± 9.3 µm, respectively. It was observed that at day 5 and 7 the average diameter of the 10% FBS micro-tissue is significantly larger than 0% FBS ($p < 0.001$). Moreover, at day 5 and 7, 1% and 5% FBS micro-

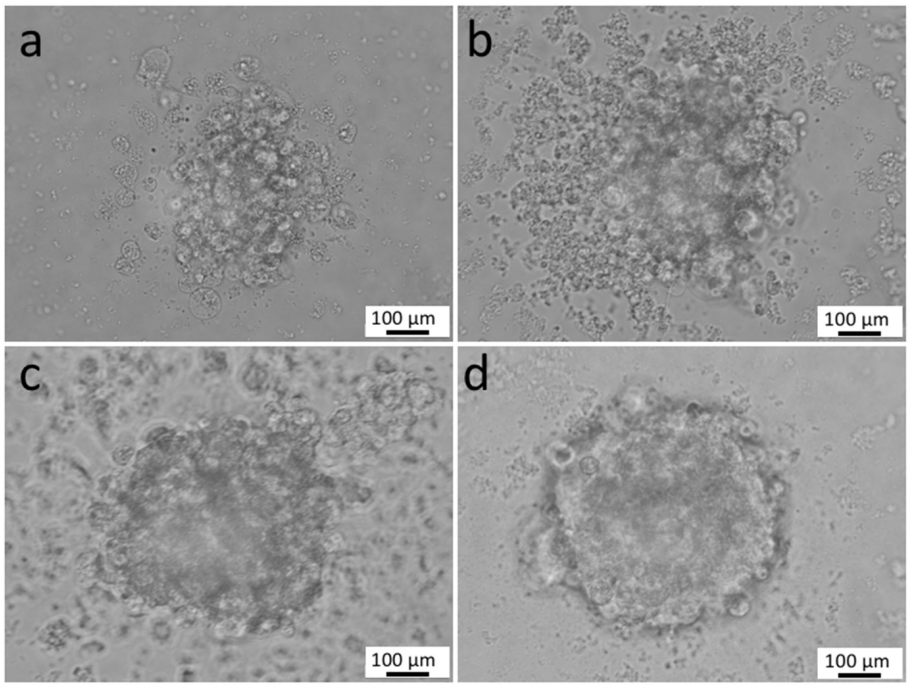

Figure 3. Micrographs of developed micro-tissues with 0% (a), 1% (b), 5% (c), and 10% (d) FBS containing media at day 7. FBS = fetal bovine serum. Scale bar represents 100 µm size..

tissue groups also formed significantly larger micro-tissues compared to 0% FBS group ($p < 0.01$). At day 3 the only significant difference was observed between 10% FBS group and 0% FBS group ($p < 0.05$). The results also indicated that the size of micro-tissues formed in 5% and 10% of FBS gradually increased from day 1 to day 7. However, the size of micro-tissues formed in 1% FBS group decreased from 5 days to 7 days. In addition, for 0% FBS group, the size of the micro-tissues continuously decreased from day 3 to day 7.

The fluorescent microscopy images showing the live and dead cells for experimental groups of 0%, 1%, 5%, and 10% FBS at day 7 were shown in Figures 5A, 5B, 5C, and 5D, respectively. Due to the thickness of micro-tissues, fluorescence microscopy images seem partially blurry. Mean fluorescence pixel intensity values for 0%, 1%, 5%, and 10% FBS groups were measured as green (G): 12.1 ± 3.2, red (R): 27.9 ± 4.4; G: 27.9 ± 4.4, R: 12.2 ± 2.9; G: 50.3 ± 5.6, R: 4.2 ± 1.4; G: 72.9 ± 9.2, R: 3,3 ± 1.2, respectively. The higher cell viability was observed in 10% FBS concentration. For instance, 10% FBS constructs revealed highest green intensity with limited red intensity. Decreasing the FBS concentration to 5% and 1%, red color intensity was increased significantly ($p < 0.01$). However, no significant difference was observed when serum concentration decreased from 10% to 5 %. Furthermore, 0% FBS micro-tissues showed highest red color intensity with lowest green intensity at day 7.

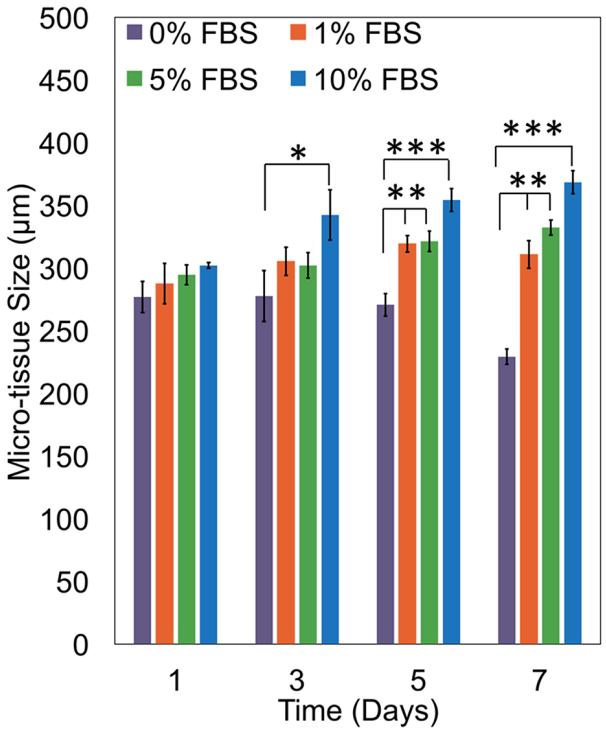

Figure 4. Effect of 0%, 1%, 5%, and 10% FBS containing media on the size of the micro-tissues at 1, 3, 5, and 7 day. FBS = fetal bovine serum,*p < 0.05, **p < 0.01, ***p < 0.001.

Discussion

Scaffolds usage for developing 3D micro-tissues generally fails to mimic the required functions of the natural ECM. Additionally, cell-scaffold interaction often inhibits cell-cell communications that has a major function on 3D tissue formation. Scaffold-free micro-tissue development studies have become a strong alternative to the use of synthetic scaffolds and mostly focus on understanding the mechanisms of *in vivo* like tissue formation to further investigate either discovered drugs or tissue engineering purposes [14]. Micro-tisseues that can be grown in serum-free or as less as possible serum supplemented media could be identical for eliciting the response of drugs or biomimetic peptides to the cell line. The reason of that drug molecules have high potential to interact with the protein structures that are in the content of serum. Besides, since it is not clearly defined whole type of proteins and their concentrations in serum, it would be even harder to predict which protein causes inhibition of drug molecules if micro-tissues are tissues are intended to use in drug or biomimetic peptides effectiveness tests [15]. It was previously shown that scaffold-free micro-tissue formation led self-assembly of cells into micro-tissue by secreting their own ECM without a synthetic scaffold. Scaffold-free micro-tissue formation mostly requires high protein concentration to self-assemble of the cells. The main protein source in cell culture media is FBS. FBS is defined as a natural cocktail that contains most of the required factors for micro-tissue formation. However, not fully characterized and batch-to-batch variation, biosafety aspects, and limited availability characteristics limit the usage of FBS in cell culture application [16]. Furthermore, due to the not fully characterized rich content of FBS, effect of individual parameters such as different extracellular matrix proteins, biomimetic peptides, and growth factors on micro-tissue formation cannot be determined if micro-tissue formation occurs in the presence of FBS. Therefore, the present study examined the effect of FBS concentration on scaffold-free micro tissue formation. Moreover, this study also showed the

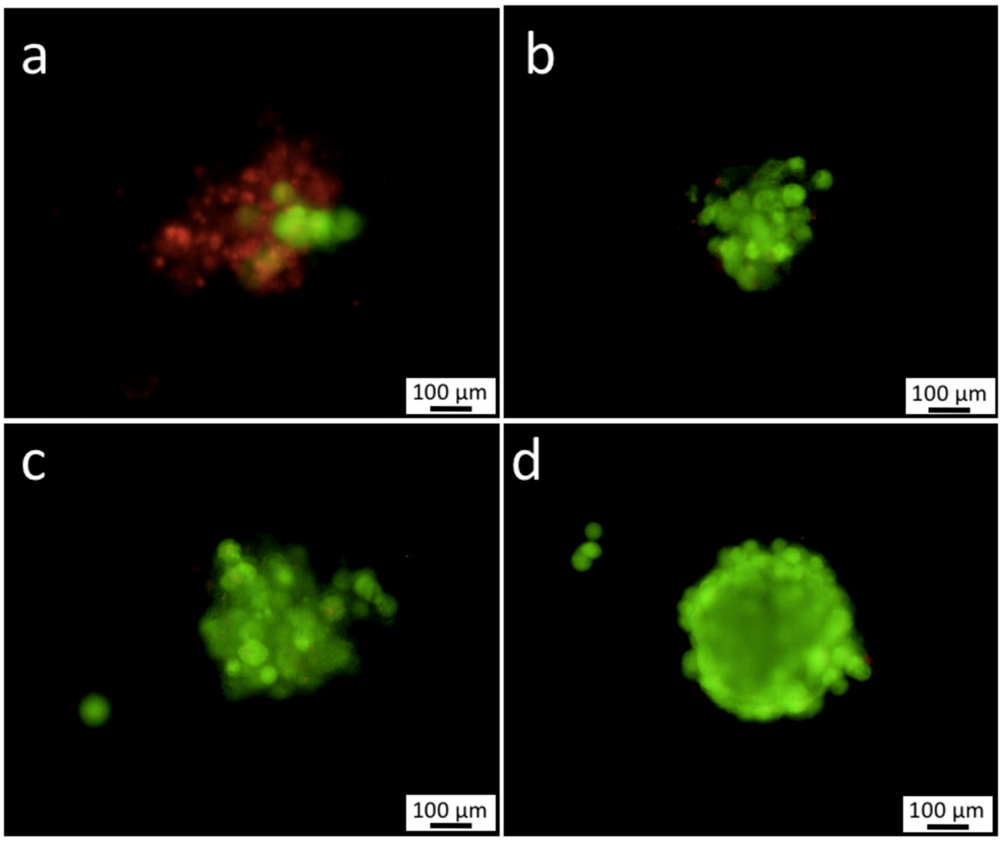

Figure 5. Viability of cells within the micro-tissues for 0% (a), 1% (b), 5% (c), and 10% (d) FBS groups was examined on day 7 (green: LIVE cells, red: DEAD cells) (20×). Scale bar represents 100 µm size. FBS = fetal bovine serum..

minimal required FBS concentration to develop scaffold-free micro-tissues and effect of FBS concentration on cell viability during micro-tissue formation.

The micro-tissue development was successfully performed by 3D petri dish protocol as explained in the methods section. Micro-molded agarose guides spontaneous self-assembly of HUVECs into 3D spheroids which also can be called microtisseues [17]. High FBS content 10% of culture media used as a positive control in this study. The micrographs shown in Figures 1E and F confirms *in vitro* 3D micro-tissue formation. As depicted from figure 1G, cell viability was quite high when 10% FBS concentration was used. Similarly, it was previously reported that 10% FBS usage in cell culture media resulted with spherical micro-tissue formation with high cell viability. Figure 2 represents the initial micro-tissue like formations on day 1 after the culture initiated. The average sizes of the constructs were quite close and no significant difference was observed among the 0%, 1%, 5% and 10% FBS groups. Such results can be explained as on day 1, HUVECs self-assembled into micro-tissue like constructs but the proliferation phase has not started. Since the initial cell numbers for each group was similar, it was meaningful to reach similar size of the constructs.

Micro-tissue size assessment with time data also confirms that at early time points FBS concentration was not a vital issue; however, at day 5 and 7 it was clearly observed that with 0% and 1% FBS groups showed decreased size of the micro-tissue. Although the micro-tissue formation completely disturbed after 3 days, early time points of the culture data revealed that initially micro-tissue like constructs were self-assembled even with 0% and 1% of FBS. Similar to our results, Dissanayaka et al. [9] observed significant increase on micro-tissue diameter from day 3 to day 7 when cultured in 10% FBS supplemented EGM media. One possible explanation for such trend could be the limited proliferation of cultured HUVECs with limited protein sources. Similarly, live/dead staining assay was also confirmed that 0% and 1% FBS groups demonstrated high number of dead cells in micro-tissues. As depicted from Figure 5, 5% and 10% FBS supported healthy micro-tissue formation with high ratio of live cells. These results were in agreement with Sanz-Nogués and O'Brien [18] where they indicated the requirement of using low FBS concentrations to understand the vascularization of endothelial cells even in 2D culture. Furthermore, Rouwkema and Khademhosseini [14] also suggested

that biological cues that guides the vascularization process in tissue engineered scaffolds needs to clearly identified to understand major factors in vascularization. Taken together, recent results clearly showed that HUVECs initiated micro-tissue like formation even with limited FBS concentration at early time points; however, proliferation was significantly affected from the absence of required proteins in the culture. Therefore, addition of the biological cues such as individual growth factors and bioactive peptide structures into the culture that does not include FBS to understand vascularization process of scaffold-free micro-tissues could guide the vascular tissue engineering society.

Conclusions

In summary, the present study described the effect of FBS concentration on *in vitro* development of scaffold-free micro-tissue. The results confirmed that micro-tissue formation and cellular viability are directly related to the FBS concentration. The concentration of required proteins in FBS play vital role in cell viability and growth of micro-tissue. Furthermore, since the aim of the study is to clarify the minimum FBS content supplemented media to grow micro-tissues, due to the successful development of micro-tissues in 0% and 1% FBS groups, such concentration could be identical for determining the efficacy of biomimetic peptides and different extracellular matrix proteins on micro-tissue formation parameters of HUVEC. High cell viability in micro-tissues was observed with 5% and 10% serum concentration.

Authorship declaration

All authors listed meet the authorship criteria according to the latest guidelines of the International Committee of Medical Journal Editors, and all authors are in agreement with the manuscript.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript. The authors alone are responsible for the content and writing of this article.

Ethical Statement

There are no animal experiments carried out for this article.

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The effect of *Arnebia purpurea* extract on the survival of random pattern skin flaps in rats

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ABSTRACT

Objectives. One of the important causes of flap losses is ischemia-reperfusion damage. *Arnebia* species are rich in naphthoquinone derivatives which known to have anti-inflammatory and anti-oxidant effects. The aim of the present study was to investigate the effects of *Arnebia purpurea* extract on viability of the skin flaps. ***Methods.*** Eighteen Wistar rats were divided in three groups. Caudal-based 9×3 cm size skin flap was applied on dorsum of the all rats and following surgery, 2 cc of *A. purpurea* extract topically was applied to the group 1 and 2 cc of 0.2% Nitrofurazon cream topically was applied to the group 2, daily. The Group 3 only received flap surgery (control group). Seven days later, all subjects were euthanatized and necrosis rate in their flaps was calculated and compared to each other. ***Results.*** The necrosis rate was calculated as 20.25% ± 1.59% in Group 1, 32.05% ± 2.23% in the Group 2 and 37.33% ± 4.12% in the Group 3. It was found that necrosis rate in the Group 1 was statistically significantly less than Groups 2 and 3 ($p < 0.001$) and that difference in necrosis rate between Group 2 and Group 3 was not statistically significant ($p > 0.05$). ***Conclusion.*** Necrosis of skin flaps was reduced through topical application of *A. purpurea* extract.

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Keywords: Arnebia purpurea, skin flaps, necrosis, naphthoquinones, plant extracts

Introduction

The flaps have been used for repair of tissue defects and partial or complete tissue loss still remains as an important problem despite technological advanced in time and advanced techniques. One of the important causes of flap losses is ischemia-reperfusion damage. Ischemia is a condition during which part of a certain tissue receives insufficient blood supply [1]. If ischemia lasts longer than the tissue tolerates then necrosis occurs. If reperfusion is achieved before necrosis occurs, several physiopathological events occur which are first reversible and then become irreversible as a consequence of continuing condition, leading to so-called ischemia-reperfusion (I-R) damage. Main reason for I-R damage is reactive

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oxygen species and inflammation [2].

Many pharmacological agents such as sympatholytics, vasodilators, prostaglandin inhibitors, glucocorticoids, anti-coagulant, and free radical scavenging agents have been used experimentally to ischemia and I-R damage to the skin flaps and flap viability but no clinically usable method has been developed for this purpose so far [3, 4].

Chemicals found in nature have been used for therapeutic purposes since ancient times. Despite competition from other drug discovery methods, natural products are still providing their fair share of new clinical candidates and drugs. Natural products are still a significant source of new drugs, especially for anticancer, antimicrobial, and antihypertensive therapies [5].

Alkanna in Europe and North Africa, Lithospermum in far-east and Arnebia in Anatolia has been used for centuries in traditional medicine [6]. All of them are members of *Boraginaceae* family and roots of the plants in *Boraginaceae* family are rich in naphthoquinone [7]. Naphthoquinone are used by industry as drug and food dye [8]. Naphthoquinone derivatives, Shikonin (R-configuration) and its enantiomer alkannin (S-configuration) has been shown to have wide variety of biological properties including accelerated wound healing, anti-oxidant, anti-bacterial, anti-fungal, anti-viral, anti-inflammatory , anti-tumor effects [9-13]. Previously we showed that the roots of *Arnebia purpurea* which is one of the *Boraginaceae* family member in Turkey contain high amounts of naphthoquinones [14]. Our hypothesis is the roots of *A. purpurea* which contain high amounts of naphthoquinones may reduce I-R damage on flap by anti-oxidant effects. In this study, we aimed to demonstrate the effects of *A. purpurea*'s root extract on viability of the skin flaps.

Methods

Approval was taken for the present study from the University Local Ethics Committee for the Experimental Animals. The study was conducted in the Production and Research Laboratories for Experimental Animals of University. Eighteen female Wistar Albino rats weighting between 250 and 350 grams produced in the Production and Research Laboratories for Experimental Animals of University. There are no differences on weight measurements of animals in the groups. The rats were housed in appropriate cages at 20°C and under 12 hours of light and dark periods. The animals were kept in separate cages in order to keep them from harming to each other prior to the surgical procedure. All rats were fed on standard rat food and no water restriction was applied.

Preparation of the extract of A. purpurea

Plant Material

The roots of *A. purpurea* were collected from Taşkent, Konya, Turkey. The plant was collected, identified and authenticated by Prof. Dr. H. D. and Dr. B. B (Department of Biology, Faculty of Sciences, Gazi University). A voucher specimen (No 3765) has been deposited in Faculty of Science, Gazi University.

Preparation of Plant Extract

The dried and powdered roots of *A. purpurea* (300 g) were extracted with n-hexane (3×500 ml, 40˚C). Each extract was collected and evoporated under reduced pressure at a temperature below 40˚C to yield dark red viscous residue (*A. purpurea*, 8.5 g).

Preparation of Cold Cream Formulation

n-hexane extract from the root of *A. purpurea*, was used as 1% concentration which was dissolved in cold cream. The cream formulation was prepared briefly as follows; 12.5 g cetyl esters wax, 12.5 g white wax, 56 g mineral oil, 0.5 g sodium borate and 19 g purified water were accurately weighed to obtain about 100 g cold cream formulation. Cetyl esters wax and white wax were reduced to small pieces and melted on a steam bath. Mineral oil was added and the mixture was heated until the temperature reached 70 °C. 1 g active extract was then added to the oily phase and mixed. Sodium borate was dissolved in purified water, warmed to 70 °C and gradually added to the melted mixture. It was stirred rapidly and continuously until congelation as described in the USP United States of Pharmacopeia. For control group, same cold cream was prepared but 1 g Nitrofurazon (Furacin®) was added instead of *A. purpurea* extract.

Surgical Procedure

All surgical procedures were performed with intramuscular administration of 50 mg/kg ketamine-HCl (Alfamine®: Ege-VET) and 10 mg/kg xylazine HCl (Rompun®: Bayer) for anesthesia by the same surgeon under sterilized conditions. The rats were fixed in prone position after their back had been

shaved. Surgical site was cleaned with 10% povidon iodine solution and covered sterilely. From their back, modified McFarlane flap included panniculus carnosus of 9×3 cm in size was removed and then flap was re-sutured with 4/0 nylon sutures [15].

The animals were divided in 3 groups so that each group contains 6 rats. Group 1 (*Arnebia purpurea* group): Following surgery 2 cc of *A. purpurea* cream was applied topically daily on the flap. Group 2 (Nitrofurazon group): Following surgery, 2 cc of 0.2% Nitrofurazon (Furacin®) cream was applied topically daily on the flap. Group 3 (control group): No substance was applied on the flap.

Evaluation of Flap Size

On the 7th day after the flap surgery all subjects were euthanized with high doses anesthesia. All flaps' photographs were taken from the same distance (60 cm) with a Sony DSC-F828 camera (Sony Corporation, Tokyo, Japan) by a different researcher who was blind about groups. The total area of necrosis was determined using the percentage of flap viability was calculated using the program Adobe Photoshop CS 5 (Adobe Systems, Inc., San Jose, CA). The necrotic area was marked on the software and the area was noted in pixels and then the percentage was calculated by a different researcher who was blind about groups [16].

Statistical Analysis

Data analysis was performed using the package program IBM SPSS Statistics 17.0 (IBM Corporation, Armonk, NY, USA). Normality of distribution of the continuous variables was tested using Shapiro-Wilk's test and homogeneity of the variances was tested using Levene's test. Definitive statistics were presented as mean ± standard deviation. Significance of the difference in ratio of necrotic area to the total area between the groups was examined with one-way analysis of variance (one-way ANOVA). In the case of significant difference being detected in one-way ANOVA, multiple comparisons of the groups were performed using with Tukey's test. A p value less than 0.05 was considered as statistically significant.

Results

Mean necrosis rate in Group 1 (*A. purpurea* group) was 20.25% ± 1.59%, in Group 2 (Nitrofurazon group) was 32.05% ± 2.23% and in group 3 (control group) was 37.33% ± 4.12% (Figures 1 and 2). Necrosis rate in the Group 1 (*A. purpurea* group) was statistically significantly less than Groups 2 (Nitrofurazon group) and Group 3 (control group) (p<0.001) and that difference in necrosis rate between Group 2 and Group 3 was not statistically significant (p=0.150) (Table 1).

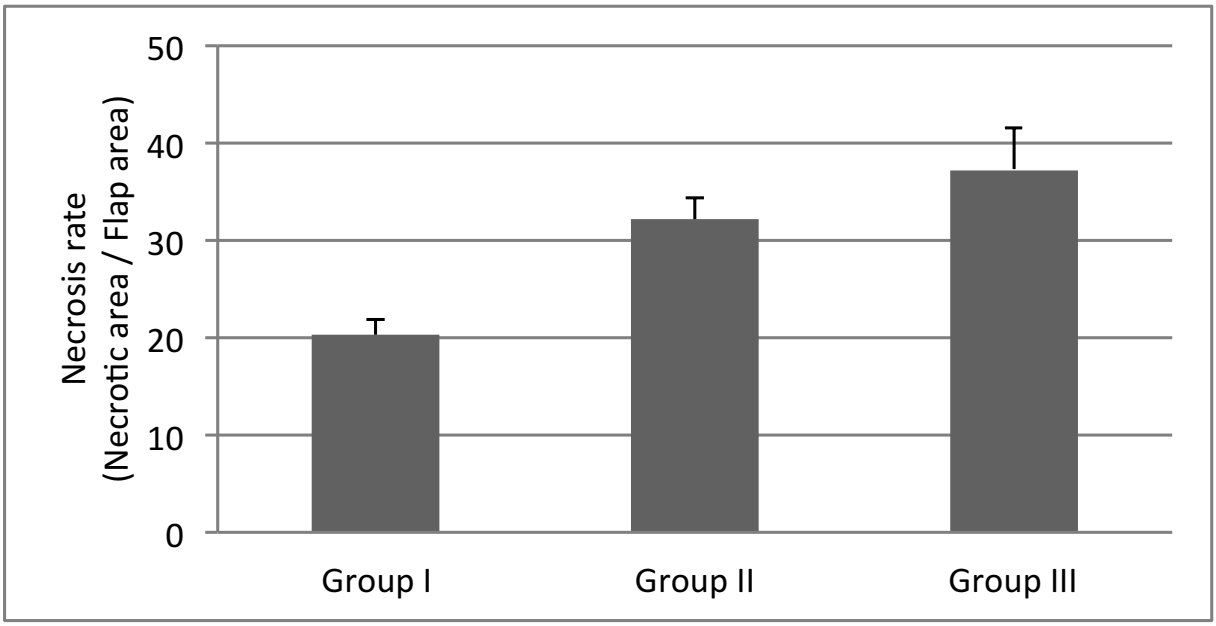
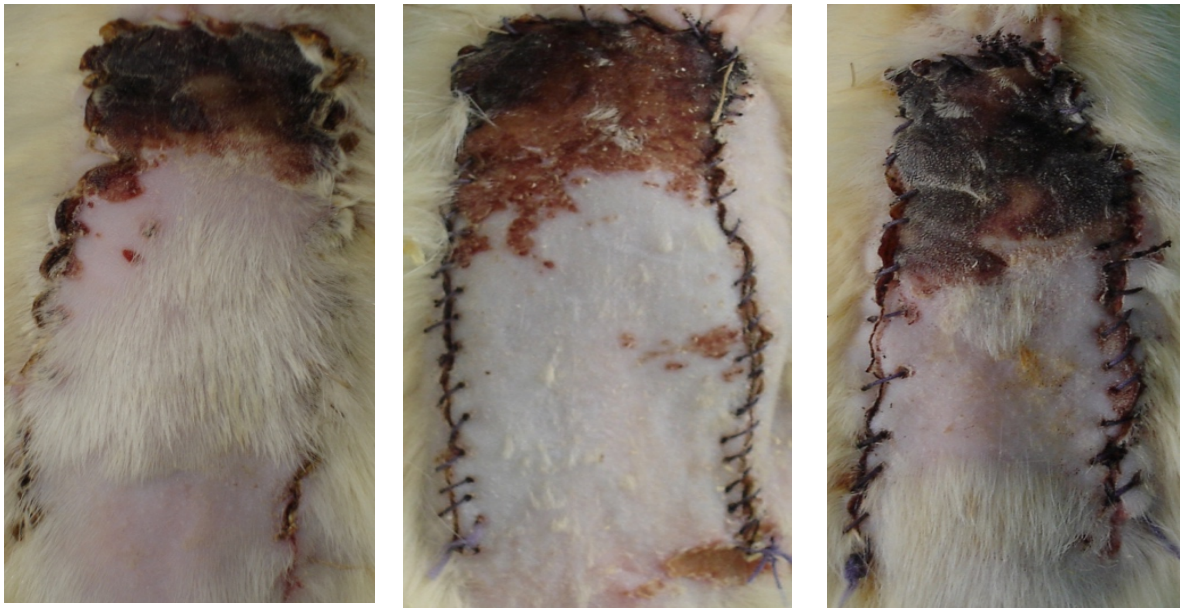


Figure 1. Mean necrosis rate of groups. Necrosis rate in Group I (*Arnebia purpurea* group) was statistically significantly lower than the Group II (Nitrofurazon group) and Group III (control group) (p <0.001) (post hoc Tukey's test)



a b c

Figure 2. View of necrosis of the flaps. a = Group 1 (*Arnebia purpurea* group), b = Group 2 (Nitrofurazon group) and c = Group 3 (control group).

Discussion

Previously we showed that the roots of *A. purpurea* involve naphthoquinones highly [14] and in the current study we think that because of anti-inflammatory and anti-oxidant activity, naphthoquinone derivatives in the *A. purpurea* extract reduced I-R damage occurring in the flap so amount of necrosis was found to be statistically significantly lower in the groups receiving *A. purpurea.*

In the experimental model of caudal-based randomly patterned skin flap on back of the rats we used in the present study, no tissue loss occurred on the area close to the pedicle when the flap was removed because it had sufficient perfusion but irreversible tissue damage and necrosis occurred due to ischemia at the tip of flap away from the pedicle. In so-called transitional zone between these areas, ischemia occurred in early stage due to hyperadrenergic condition because of noradrenaline released from the sympathetic nerve endings intersected during flap removal but perfusion was regained in 12 to 24 hours after the hyperadrenergic condition ended. Reperfusion occurring after ischemic period causes ischemic-reperfusion damage [3].

Basic role in physiopathology of I-R damage is played by reactive oxygen species (ROS) During ischemia period, high amount of xanthine oxidase-mediated ROS from endothelial cells and during

Table 1. Mean necrosis rate of groups

	Necrosis Rate (%)
Group 1	20.25 ± 1.59
Group 2	32.05 ± 2.23
Group 3	37.33 ± 4.12
p^a	< 0.001
Group 1 - Group 2	$p < 0.001^b$
Group 1 - Group 3	$p < 0.001^b$
Group 2 - Group 3	$p = 0.150^b$

Data are shown as mean ± standard deviation. Group I = *Arnebia purpurea* group), Group II = Nitrofurazon group, Group III = control group, [a] one-way analysis of variance (One-way ANOVA), [b] post hoc Tukey's test

reperfusion period high amount of nicotine amide adenine dinucleotide phosphate (NADPH) oxidase-mediated ROS from neutrophils generated in skin flap. ROS damage to DNA by oxidizing the nucleic acids, impair protein structure by oxidizing the amino acids, and cause lipid peroxidation by reacting with fatty acids [4, 6].

Shikonin/alkannin which are naphthoquinone derivatives, gives electron to the reactive oxygen radicals and make them more stable, reduces lipid peroxidation, increase amount of such anti-oxidant enzymes as superoxide dismutase (SOD), catalase (CAT), and glutathione (GSH), prevents attraction of the neutrophils by reducing capillary permeability, and decreases neutrophil derived ROS release by inhibiting the NADPH oxidase enzyme in the neutrophils [6, 17] and through anti-oxidant activity occurring this way, shikonin/alkannin reduces I-R damage [17].

Rohrich *et al.* [18] defined an ideal pharmacological agent to be used to improve viability of the flap as being able to exert effects in the post-operative period, being easy to apply, reliable, cheap, having fully clarified mechanism of action, and protective effects against flap necrosis. *Arnebia* extracts have been used in traditional medicine for centuries and thus is reliable. Herbal products can be prepare as easy and cheap. As in traditional medicine, it was used in the present study topically and its topical use was shown to be effective.

Although we think that *A. purpurea* increases flap viability with antioxidant effect but as a limitation of our study, we didn't have any analysis about it so our study should be accepted as preliminary work and further studies on the mechanism of that flap protective effect are needed.

Conclusions

In conclusion, in this study we showed that with high naphthoquinones content, *A. purpurea* cream decreased randomly patterned flap necrosis.

Authorship declaration

All authors listed meet the authorship criteria according to the latest guidelines of the International Committee of Medical Journal Editors, and all authors are in agreement with the manuscript.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Effectiveness of trospium chloride and doxazosin mesylate combination in neurogenic bladder patients with spinal cord injury

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ABSTRACT

Objective. The aim of this study was to compare the effects of trospium chloride (TCL) and TCL + doxazosin (DXZ) combination to bladder capacity and residual urine volume (RUV) in spinal cord injury (SCI) patients with neurogenic bladder. ***Methods***. The study included 120 patients with SCI. Urodynamic data of patients were reviewed retrospectively. Changes in maximum cystometric capacity (MCC) as well as RUV were determined in patients using 60-90 mg/day TCL (Group 1, n = 98) or 60-90 mg/day TCL + 4-6 mg/day DXZ (Group 2, n = 22). ***Results***. There was statistically significant increase in both MCC and RUV values in both groups. There was no statistical difference in MCC and RUV values in Group 1 and Group 2 (p=0.111 and p=0.664, respectively). There was a significant weak negative correlation between duration of injury and MCC values (r = 0,185; p=0.043), meaning as the duration of injury increased, MCC decreased. There was no statistically significant correlation between medication usage duration with MCC and RUV (r = -0.129; p=0.159 and r = -0.68; p=0.462, respectively). ***Conclusions***. Anticholinergic treatment is currently the mainstay conservative treatment of neurogenic detrusor overactivity. The impact of alfa blockers on neurogenic bladder has been less well evaluated. We consider that, adding DXZ to TCL has no additional benefit to increase bladder capacity and reduce RUV. Further studies are needed to determine the location of DXZ treatment in SCI patients with neurogenic bladder.

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Keywords: spinal cord injury, neurogenic bladder, doksazosin mesylate, trospium chloride

Introduction

In suprasacral spinal cord injuries (SCI), the sacral and pontine micturition centers are separated, and reflex voiding is initiated by an involuntary detrusor contraction rather than relaxation of the external urethral sphincter. Urologic complications are associated with increasing bladder pressures [1]. Neurogenic bladder (NB), which occurs in 70-84% of patients with SCI, is a high-risk factor for renal dysfunction and at the same time reduces quality of life [2, 3]. Therefore, NB treatment should be

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managed appropriately in order to improve quality of life and preserve renal function. The 2006 Consortium for Spinal Cord Medicine Clinical Practice Guidelines on Bladder Management has identified three main goals for the management of bladder treatment in patients with SCI. Preservation of the upper urinary tract, minimization of lower urinary tract complications, and compatibility with the patient's lifestyle [4]. Treatment of NB if not managed appropriately, life threatening complications may occur such as vesicoureteral reflux, urinary tract infections, nephrolithiasis, hydronephrosis and renal failure. Conservative treatment is the first choice in almost all cases and will continue to be the primary choice in the majority of NB patients. Anticholinergics are the first-line choice for treating neurogenic detrusor overactivity. The mode of action of anticholinergic drugs is not clear. However, it is believed that drugs reduce detrusor overactivity and block muscarinic receptors, resulting in resistance to parasympathetic stimulation. This action results in improved bladder compliance and reduced symptoms of overactive bladder [5]. Alpha adrenergic receptors have been identified in the proximal urethra, prostate, and bladder neck. Alpha-blockers have been found to lower urethral resistance and improve voiding. Alpha-blockers seem to be effective for decreasing bladder outlet resistance, residual urine volume (RUV), and autonomic dysreflexia [4]. Doxazosin (DXZ) is an alpha-1 adrenergic blocker and contributes to the treatment of NB due to SCI by performing the above effects. Trospium chloride (TCL), is a quaternary amine with a low oil-to-water partition coefficient, poor absorption from the gastrointestinal tract with low bioavailability and poor central nervous system penetration [6]. The aim of this study was to compare the effects of TCL and TCL + DXZ combination to bladder capacity and RUV in SCI patients with NB.

Methods

One hundred and twenty patients (94 male, 26 female) who were on rehabilitation program in our hospital with the diagnosis of SCI with NB were studied retrospectively. After retrospective screening, patients at spinal shock period; patients who underwent urodynamic study before; patients with previous lower urinary system disease, individuals with NB due to other causes (diabetes mellitus, previous stroke or brain injury, other neurologic diseases etc.), patients with SCI out of lesion level, brain injury and pelvic trauma accompanying to SCI and previously used pharmacological agents for the urinary bladder such as anticholinergics, alpha-blockers, baclofen and injections were not included in the study. The study protocol was approved by the ethical committee of our institution. Patients were assessed based on the results of two consecutive urodynamic tests with a time interval of no more than 2 months. The patients were divided into two groups using only TCL 60-90 mg/day (Group 1, n = 98) and TCL 60-90 mg/day + DXZ 4-6 mg/day (Group 2, n = 22). Changes in maximum cystometric capacity (MCC) as well as RUV of patients were determined in both groups. For urodynamic testing, a computer-assisted urodynamic unit (Libra + MMS, Enschede, The Netherlands) was used in all patients. The bladder was filled and the intravesical pressure was recorded via a sterile transurethral double-lumened 8 F catheter. Sterile saline solution at body temperature was used as a filling medium, and the bladder was filled at a rate of 50 ml/min. MCC was defined as a patient experienced sensation that would normally lead to immediate evacuation of the bladder, the volume at the time as intravesical pressure was above 40 cmH20 and the volume at the time as the beginning of voiding without control [7].

Statistical Analysis

The statistical analysis was performed using SPSS-15.0 and level of statistical significance was defined as $p < 0.05$. Descriptive statistics, paired-samples t test, Pearson correlation test and independent-samples t test were used.

Results

Mean age of the patients was 34.95 ± 13.61 years, mean duration of injury was 13.17 ± 30.49 months and medication usage duration was 2.57 ± 1.93 months. In Table 1, demographic properties of the patients and in Table 2, both groups' MCC and RUV levels were shown. There was no significant difference between groups in terms of duration of injury, age and medication usage duration. There was statistically significant increase in both MCC and RUV values in both groups. There was no statistical difference in MCC and RUV in Group 1 and Group 2 (MCC: 148 ml vs. 83 ml; $p = 0.111$ and RUV: 141 ml vs. 122 ml; $p = 0.664$). There was a significant weak negative

Table 1. Characteristics of the groups

Characteristics		Group 1 (n = 98)	Group 2 (n = 22)	*p*
Age (year)		34.5 ± 13.3	36.6 ± 14.93	0.510
Sex	**Female**	23 (23.5%)	3 (13.6%)	0.420
	Male	75 (76.5%)	19 (86.4%)	
Neurological level	**Cervical**	10 (10.2%)	1 (4.5%)	0.371
	Thoracic	66 (67.3%)	13 (59.1%)	
	Lumbar	22 (22.5%)	8 (36.4%)	
Etiology	**Gun injury**	9 (9.2%)	1 (4.5%)	0.108
	Traffic accident	39 (39.8%)	5 (22.7%)	
	Falling	36 (36.7%)	8 (36.4%)	
	Others	14 (14.3%)	8 (36.4%)	
Duration of injury (month)		12.95 ± 3.39	16.50 ± 35.73	0.633

Data are shown as mean ± standard deviation or number (percent).

correlation between duration of injury and MCC values before treatment in both groups (r = 0.185; *p*=0.043), meaning as the duration of injury increased, MCC decreased. There was no meaningful correlation between medication usage duration with MCC and RUV in both groups (r = -0.129; *p* = 0.159 and r=-0.68; *p* = 0.462, respectively).

Discussion

Neurogenic lower urinary tract dysfunction (NLUTD) is an important cause of morbidity and mortality among SCI patients [8]. The condition is known to be life threatening if not properly managed. There are three main goals for the management of bladder treatment in patients with SCI. Preservation of the upper urinary tract, minimization of lower urinary tract complications, and compatibility with the patient's lifestyle [4]. Urodynamic testing will be necessary in many patients to gain more complete diagnosis of how the neurogenic dysfunction has changed the function of different components in the lower urinary tract and their interaction [9]. Drugs are often used in patients with neurogenic bladder. They aim at decreasing detrusor activity, increasing bladder capacity and/or increasing/decreasing bladder outlet resistance [9]. Anticholinergic treatment is the first-line therapy for neurogenic detrusor overactivity. This treatment works by blocking cholinergic transmission at muscarinic receptors. Anticholinergic agents have similar efficacy; however, they have different side effect and tolerability profiles that depend on their muscarinic receptor selectivity and the rate of drug distribution. Several studies have shown that anticholinergic treatment increases bladder capacity, reduces bladder pressure, and improves compliance and quality of life [10]. TCL is a quaternary ammonium derivative with mainly antimuscarinic actions, its effectiveness and safety was confirmed by meta-analysis. It does not break the blood–brain barrier. Central nervous system side effects are therefore not expected [9]. Alpha-blockers are a nonsurgical method to treat detrusor sphincter dyssynergia and low bladder pressure during voiding. Alpha adrenergic receptors have been identified in the proximal urethra, prostate, and bladder neck. Alpha adrenergic blockers have been found to lower urethral

Table 2. MCC and RUV comparison in both medication groups

	Before Treatment	After Treatment	*p*
Group 1 (n = 98)			
MCC (ml)	244.32 ± 144.83	393.30 ± 206.38	0.000
RUV (ml)	191.52 ± 148.40	332.8 ± 238.17	0.000
Group 2 (n = 22)			
MCC (ml)	271.90 ± 135.66	355.31 ± 127.09	0.001
RUV (ml)	155.00 ± 118.60	277.13 ± 187.84	0.005

Data are shown as mean ± standard deviation. MCC = maximum cystometric capasity, RUV = residual urine volume

resistance and improve voiding. Though earlier adrenergic blockers were less urologic-specific, they were commonly used for medical treatment of lower urinary tract dysfunction in individuals with SCI [11]. More specific adrenergic blockers (against alpha 1-A adrenergic receptors) are now being used to treat lower urinary tract dysfunction associated with high urethral resistance in individuals with SCI [12]. Understanding the risks, benefits, and contraindications of the different alpha-blockers will help the individual with SCI make an informed decision on the type of bladder management to be tried [4]. In 1994, Swierzerwski *et al.* [13] studied the effect of terazosin on bladder compliance in 12 spinal cord injured patients with poor bladder compliance and they found that improvement in compliance was statistically and clinically significant. After this result, they suggested that terazosin may have an effect on alpha receptors in the detrusor muscle or central effects and that improved compliance is not due to decreased outlet resistance [13]. In addition, in 1996, Yasuda *et al.* [14] studied a placebo controlled double blind trial with 136 patients with NB. They gave to patients' placebo, 30 mg or 60 mg urapadil (an alpha blocker) for 4 weeks and they found that the highest dose group showed a statistically significant decrease in urodynamic detrusor overactivity. Our study basically designed with the possible beneficial effects of alpha blockers on the NB in the direction of the above-mentioned mechanisms and studies. In our study TCL was used as an anticholinergic agent and DXZ as an alpha-blocker. Patients were divided into 2 groups as TCL 60-90 mg/day users and TCL 60-90 mg/day + DXZ 4-6 mg/day users. By separating these groups, we aimed to investigate whether DXZ may have any therapeutic effect on MCC and RUV values in addition to TCL in the direction of the above-mentioned alpha-blocker action mechanisms. At the end of our study, we found a significant increase both MCC and RUV values in both groups after treatment. However, despite the increase in MCC and RUV values, there was no statistical difference between Group 1 and Group 2 in terms of these values. In 1991, Stöhrer et al. [15] studied the urodynamic effects of TCL on SCI patients with NB and they found that TCL improved MCC. In accordance with the study of the Stöhrer *et al.* [15], we found a significant increase in MCC in both groups. So, we agree with Stöhrer *et al.* [15] that TCL has increased the MCC values. However, Groen *et al.* [2] suggested that alpha blockers seem to be effective for decreasing bladder outlet resistance, RUV and autonomic dysreflexia in neurourological patients, but we did not find a significant decrease in RUV values in Group 2. Although theoretically sharing the proposal with alpha blockers in Groen *et al.*'s study [2], we have not observed any improvement in the RUV values in our study. Administration of anticholinergic agent simultaneously may embower the RUV decreasing effect of alpha blocker in our study. However, we believe that our study is important as it gives information about anticholinergic and alpha blocker combination therapy in SCI patients with neurogenic bladder.

The Limitations of the Study

The rates of bladder filling during the urodynamic test of the patients included in the study were 50 ml / min. in our retrospective study. Although this filling rate is the upper limit of medium fill cystometry, it may provoke detrusor overactivity in SCI patients with overactive detrusors. Choosing individualized filling rate (body weight-kg / 4) would be more suitable.

Conclusions

In this study we have detected that, adding DXZ to TCL had no additional benefit to increase bladder capacity and reduce RUV. Further studies are needed to determine the location of DXZ treatment in SCI patients with NB.

Authorship declaration

All authors listed meet the authorship criteria according to the latest guidelines of the International Committee of Medical Journal Editors, and all authors are in agreement with the manuscript.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Open tibial pilon fractures: treatment with ankle-spanning Ilizarov fixator

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ABSTRACT

Objectives. The aim of this retrospective study was to report the treatment results obtained with the ankle-spanning Ilizarov fixator technique in the treatment of complex OTA/AO type 43C3 open tibial pilon fractures. ***Methods.*** A total of 14 patients with open OTA/AO type 43C3 tibial pilon fractures were evaluated. The demographics and fracture characteristics, preoperative and postoperative radiological evaluations, duration of follow-up (months), time to union (months) and complications were recorded. After collection of operative data, patients were invited for functional and radiological outcome evaluation. American Orthopaedic Foot and Ankle Society (AOFAS) scores and range of movement (ROM) of the ankle joint were investigated. Also radiologically the ankle osteoarthritis level according to the Bargon et al. criteria was noted. ***Results.*** The mean age of the patients was 48.7 years (range, 26-72 years). The mean follow-up period was 32 months (range, 25-46 months). The clinical and radiological time to union was mean 6.5 months (range, 5-11 months). On the postoperative ankle CT images, the separation within the ankle was measured as < 2mm in all patients and in 3 patients, stepping was measured as > 2mm. Following removal of the external fixator, dorsiflexion was measured as mean 15.5° (range, 0°-23°) and plantar flexion as mean 26.14° (range, 13°-36°). The mean AOFAS was 80.35 (range, 56-92). ***Conclusion.*** Satisfactory results can be obtained with the Ilizarov external fixator passing the ankle in the permanent treatment of AO-43C3 type open tibial pilon fractures.

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Keywords: pilon fracture, open fracture, Ilizarov, external fixation

Introduction

Intra-articular fractures of the distal tibia (pilon fractures) generally occur as a result of torsional movement combined with axial forces. They constitute 3%-10% of tibial fractures and 1% of all lower extremity fractures [1]. As there is thin soft tissue coverage on the tibia and when there is concomitant severe soft tissue damage, especially in complex OTA/AO type 43C3 fractures, difficulties in treatment are experienced [2, 3].

According to the soft tissue injury, there are various treatment options such as staged management with primary external fixator followed by open reduction and internal fixation, early open reduction and internal fixation, plate application with minimally invasive approachesandusing external fixators with minimally invasive reduction and fixation techniquesfordefinitive treatment [4-6]. In the current treatment of pilon fractures with concomitant soft

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tissue damage, the treatment option of external fixation with or without minimally invasive techniques is often selected because it creates fewer complications such as deep or superficial wound infection, osteomyelitis or amputation [7-9].

The aim of this study was to report the treatment results obtained with the ankle-spanning Ilizarov fixator technique in the treatment of complex OTA/AO type 43C3 open tibial pilon fractures.

Methods

This retrospective study was carried out by approval and supervision of Local Ethical Committee. Using the hospital data system, the radiographs and information forms of 113 patients who underwent surgery for tibial fractures between January 2009 and December 2015 were investigated. A total of 34 patients aged > 16 years had an acute, unilateral, open distal tibial intra-articular fracture extending to the metaphysis (OTA/AO type 43C3 tibial pilon fracture) were analyzed (Figure 1a). After exclusion of 5 patients with less than 2 years follow-up, 7 patients whose preoperative or postoperative ankle tomography images were not available and 8 patients who were treated with a technique other than ankle-spanning Ilizarov fixator technique, a total of 14 patients were included in the study for evaluation.

Demographic data including age, gender and mechanism of injury (fall from height, traffic accident, mining accident, and others) were recorded. From the emergency department examination forms and operation notes, open fractures were classified according to the Gustillo and Anderson [10]. The size of gap (measured on the preoperative and postoperative axial CT images, mm) and the size of step (measured on the preoperative and postoperative sagittal CT images, mm) between two largest fracture fragments (with using Centricity PACS-IW software, General Electric healthcare) (Figure 1b, 1c), presence/type of fibula fixation (plate, K-wire), duration of follow-up (months), time to union (months) and complications (pin site infection, malunion, osteomyelitis) were recorded. After collection of operative data, patients were invited (with phone call) for functional and radiological outcome evaluation at least one year postoperatively. At this final follow-up examination, functional evaluation using American Orthopaedic Foot and Ankle Society (AOFAS) scores and range of movement (ROM) of the ankle joint were investigated. Also radiologically the ankle osteoarthritis level according to the Bargon *et al.* [11] criteria was noted.

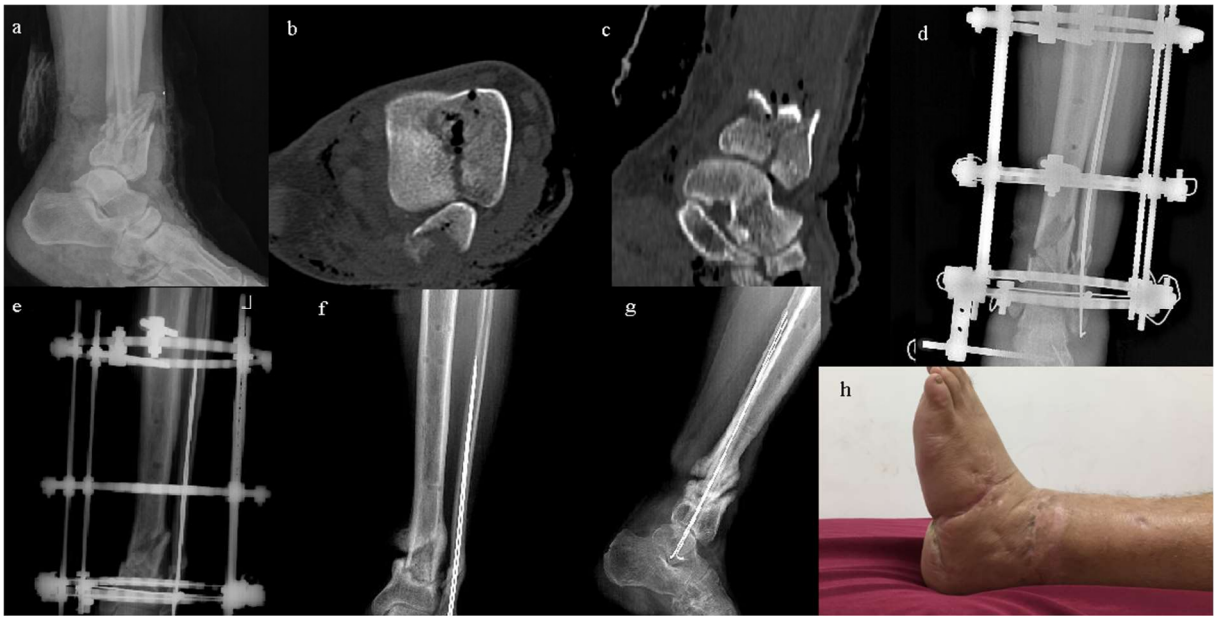

Figure 1. A 29-year-old miner (Case 4) with Gustillo and Anderson type 3a, OTA/AO-43C3 tibial pilon fracture. Lateral radiograph of the left ankle showing metaphyseal comminution (a), preoperative axial CT image of the ankle showing the gap between two largest fracture fragments (b), preoperative sagittal CT image of the ankle (c), postoperative AP radiograph after application of the ankle-spanning Ilizarov fixator (d), AP radiograph of the tibia 4 months after fixation (e), AP and lateral radiographs of the tibia six months after injury. The frame was removed. The patient was free of pain over the fracture line, with no complaints during weight-bearing. Radiological union was delayed (f and g) and active dorsiflexion of the ankle was about 0° (h).

Surgical Technique

The operations were performed by the same orthopedic surgeon. Within 8 hours of admission to the emergency department, the patients were prepared for the surgery. The frame was constructed before beginning of the surgery in the operating room. The ring sizes are selected according to the circumference of the limb allowing about two finger widths to the skin. The first two rings were arranged for placing proximal to the fracture and the third ring was arranged for placing just proximal to the ankle joint. The 3 rings were connected to each other with 4 threaded rods. With the patient in supine position, following wound debridement with saline, soft tissue was closed. Firstly the fibula was fixed closely with 2 intramedullary K-wire or openly with a 1/3 tubular plate to maintain alignment. The preconstructed Ilizarov frame was applied to the limb and fixed with wires and 5 mm Schanz screws to the tibia under fluoroscopic control. The fracture reduction of the ankle was tried to achieve closely with olive wires and ligamentotaxis and the frame was used an indirect reduction device also. The ring, which was placed just proximal to the ankle joint, was connected laterally to calcaneus with a Schanz screw (Figure 1d).

Postoperative Follow-up

Prophylactic antibiotherapy was administered to all patients for two days. The leg was elevated to decrease soft tissue swelling. Pin and wound care was done with iodine. Following the reduction of the leg edema, the patients were mobilized, but not allowed to weight bear until the 6th week postoperatively. At 6th week the Schanz screw was removed from the calcaneus and full weight-bearing was permitted with ankle exercises (Figure 1e). Clinical and radiological follow-ups were repeated every 3 weeks until union was achieved. In patients with no pain in the fracture line during the follow-up examinations and findings of union in at least 3 cortices on direct radiographs, the fixator was removed and a short-leg circular plaster cast was applied. Weight-bearing was continued with the plaster cast, which was removed after 1 month. Statistical data were expressed by the mean and range values or number and percent (Figure 1f, 1g).

Results

A total of 14 patients (9 males, 5 females) with AO-43C3 type open tibial pilon fractures were evaluated. The mean age of the patients was 48.7 years (range, 26-72 years). According to the Gustillo and Anderson classification, 4 fractures were type 3a, 3 were type 2 and 7 were type 1 open fractures. The mechanism of injury was a fall from height in 3 cases, a traffic accident in 7 and a mining accident in 3. The mean follow-up period was 32 months (range, 25-46 months). All the patients had a concomitant fibula fracture and while fixation with plate or K-wire was applied to 9 patients, fixation was not applied in 5 cases. Bone union was obtained in all patients. The clinical and radiological time to union was mean 6.5 months (range, 5-11 months) (Table 1).

In 12 (85.7%) patients there was large separation of > 2 mm and in 10 (71.4%) patients there was large stepping of > 2 mm on preoperative axial and sagittal CT images. On the postoperative ankle CT images, the separation within the ankle was measured as < 2 mm in all patients and in 3 patients, stepping was measured as > 2 mm.

Pin site infection was observed in 5 (35%) of the 14 patients and all recovered with oral antibiotic treatment. The wires were removed in 2 patients. No deep tissue infection or osteomyelitis was observed in any patient. Malunion was seen in 2 (14%) patients. Valgus angulation of approximately 11° was seen in 1 patient and posterior angulation of approximately 15° in 1 patient. No additional surgery was performed on either patient.

Following removal of the external fixator, dorsiflexion was measured as mean 15.5° (range, 0°-23°) and plantar flexion as mean 26.14° (range, 13°-36°). At the final follow-up examination, the mean AOFAS was 80.35 (range, 56-92).

On the ankle radiographs taken at the final follow-up examination, arthrosis was evaluated as grade 4 in 1 patient, grade 3 in 2 patients, grade 2 in 5 patients and grade 1 in 6 patients.

Discussion

In the treatment of high-energy pilon fractures, although the use of an Ilizarov fixator passing the ankle joint has advantages such as providing indirect reduction with ligamentotaxis, allowing the fixation of intra-articular fragments with very small incisions, no need for soft tissue dissection and allowing the possibility of stable and permanent fixation, there can also be said to be the disadvantage of discomfort for

Table 1. Data of the patients

Number	Age/sex	Mechanism of injury	Open fracture type*	Presence/type of fibula fixation	Follow-up (months)	Ankle movement (dorsiflexion/ plantar flexion)	AOFAS	Union time (months)	Ankle osteoarthritis level**	Complication
1	47/m	fall from height	1	plate	28	7/16°	65	6	4	Pin-track infection.
2	49/m	other	3a	plate	32	9/14°	56	11	3	Pin-track infection.
3	68/m	traffic accident	1	none	41	18/24°	86	5	1	malunion
4	29/m	mining accident	3a	K wire	26	0/13°	76	9	2	Pin-track infection.
5	49/m	traffic accident	1	plate	46	22/32°	92	5	1	none
6	43/m	mining accident	2	plate	25	21/34°	90	5	1	none
7	38/f	traffic accident	1	none	27	19/28°	84	6	2	none
8	58/f	fall from height	1	K wire	25	21/36°	92	5	1	none
9	26/m	traffic accident	2	none	33	17/27°	78	6	2	Pin-track infection.
10	38/f	traffic accident	3a	K wire	29	10/25°	70	6	3	malunion
11	55/m	fall from height	3a	plate	42	11/23°	74	10	2	Pin-track infection.
12	67/f	traffic accident	1	none	44	18/28°	82	7	2	none
13	72/f	traffic accident	1	none	25	23/32°	90	5	1	none
14	43/m	mining accident	2	plate	25	21/34°	90	5	1	none

*According to the Gustillo-Anderson Classification,**According to the Bargon *et al.* [11] criteria. (Grade 1: no osteophytes, no joint space narrowing; Grade 2: small osteophytes, no joint space narrowing; Grade 3: moderate osteophytes, joint space narrowing; Grade 4: large osteophytes, severe joint space narrowing)

the patient [12, 13]. Due to the frequent occurrence of complications such as wound problems, infection and osteomyelitis in high-energy open pilon fractures, anIlizarovexternal fixation method was selected in the permanent treatment of the patients in this study [14-16].

Although there are few studies that have reported the joint reduction quality following surgery of high-energy pilon fractures, in a study of 30 patients treated with Ilizarov external fixator, Osman *et al.* [17] reported that acceptable reduction was obtained in 46.6% and poor reduction in 20%. In another study of 17 patients, Kapoor *et al.* [13] reported that in 4 patients with AO-43C3 type open tibial pilon fractures, acceptable joint reduction was obtained with Ilizarov external fixator passing the joint. In the current study, although the patient number was greater, while small separation of < 2mm was achieved in all, stepping in the joint of >2 mm could not be prevented in 3 patients.

Prospective randomized studies which have compared internal fixation and external fixation in high-energy pilon fractures have reported that significantly fewer complications were seen in patients applied with external fixation [14, 18, 19]. Following treatment made with Ilizarov external fixator in 21 cases of complex tibial pilon fracture, 9 of which were open fractures, Vidyadhara and Sharath [20] reported that superficial pin site infection developed in 7 patients and deep pin site infection in 1, but no information was given about whether or not these were patients with open fractures. Okcu and Aktuglu [9] compared 44 patients with AO-43C3 type tibial pilon fractures treated with Ilizarov external fixator passing and not passing the ankle joint. It was reported that 12 patients had an open fracture and no osteomyelitis developed in any patient without differentiation of open and closed fractures, malunion developed in 10 patients and pincer toe developed in 6 patients [9]. In the current study, no osteomyelitis was observed, but there was pin site infection in 5 patients and malunion in 2.

Ankle dorsiflexion movement > 10° is usually sufficient for walking [21]. Kapoor *et al.* [13] reported that of 17 patients with high-energy pilon fractures treated with Ilizarov external fixator passing the ankle, 75% had ankle dorsiflexion of > 10°, dorsiflexion was 0° in 2 patients, plantar flexion was > 30° in 11 patients and < 20° in 1. With a mean functional score of 79.8, 4 patients with C3 fractures were reported as

acceptable. In the current study, the mean dorsiflexion was measured as 15.5° (range, 0°-23°) and plantar flexion as mean 26.14° (range, 13°-36°) and the mean AOFAS was 80.35 (range, 56-92). The ROM values and functional scores of the patients in the current study are consistent with literature. Bone *et al.* [22] stated that ankle ROM remaining at an acceptable levelafter Ilizarov external fixator treatment was associated with the distraction made to the joint by the fixator during treatment causing tension in the ligaments and prevents shortening in the ligaments.
In 30 patients with high-energy tibialpilon fractures treated with Ilizarov external fixator by Osman *et al.* [17], arthrosis developed in the joint in 11 patients, but no information was given about the grade of arthrosis. Fırat *et al*. [23] compared the Ilizarov external fixator techniques of fixed to the ankle and jointed at the ankle in 34 patients operated on for tibial pilon fracture. Post-traumatic arthrosis was reported in 31.3% of the patients with Ilizarov external fixator jointed at the ankle and in 55.5% of the patients with the Ilizarov external fixator fixed at the ankle. Again, no information was given about the degree of arthrosis. Wyrsch *et al.* [14] treated 20 of 38 patients with pilon fractures with external fixator combined with internal fixation using a minimal incision and while no osteoarthritic change was determined in only 1 patient, osteoarthritic changes were observed at a mild level in 6 patients, at an evident level in 8 and at a severe level in 4. Similarly, Guo *et al.* [24] applied external fixator combined with internal fixation with a minimal incision to 26 patients with Rüedi-Allgöwer type 3 fractures and reported osteoarthritic changes in all the patients. Calori *et al.* [1] reported that the osteoarthritic changes that developed following high-energy pilon fractures were associated with the cartilage damage that was created during the trauma and arthrosis could develop despite anatomic joint reconstruction obtained radiographically. Elsoe *et al.* [23] indicated that35% of their patients had osteoarthritis at the ankle joint following a distal intra-articular fracture 12 months after frame removal. In the current study, osteoarthritic changes of varying degrees were seen in all patients and were graded.

The Limitations of the Study

Limitations of this study can be said to be that it was retrospective, that despite a sufficient number of patients with pilon fractures, a small number of patients had open AO-43C3 type fracture, and because there was no comparison with any other treatment option, there was insufficient statistical evaluation.

Conclusions

Although several techniques have been compared in the treatment of high-energy pilon fractures, there is no standard surgical technique that is applied. The results of this study have demonstrated that satisfactory results can be obtained with the Ilizarov external fixator passing the ankle in the permanent treatment of AO-43C3 type open tibial pilon fractures.

Authorship declaration

All authors listed meet the authorship criteria according to the latest guidelines of the International Committee of Medical Journal Editors, and all authors are in agreement with the manuscript.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Intradiscal electrothermal therapy for chronic discogenic low back pain: a comparison of two heating protocols

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ABSTRACT

Objectives. This study aims to evaluate the effect of intradiscal electrothermal therapy (IDET) applied in patients with chronic low back pain using two heating protocols. ***Methods.*** In this study, data of 50 patients who were exposed to percutaneous IDET using two heating protocols were retrospectively analyzed. The patients were divided into two groups: in Group 1 (n=25), maximum 750C catheter tipping was used, while in Group 2 (n=25), maximum 900C catheter tipping was performing. Pre-treatment (M0) and post-treatment results at 3 (M3), 6 (M6), 12 (M12), and 18 months (M18) were evaluated using the visual analogue acale (VAS), Oswestry disability index (ODI), and short form-36 (SF-36) scores. ***Results.*** There was no statistically significant difference in demografic characteristics and M0 VAS, ODI values and SF-36 dimensions of the patients between the groups ($p > 0.05$). It was found that there were statistically significant improvement than baseline values in the M3, M6, M12, and M18 VAS, ODI, and SF-36 scores in both treatment groups ($p < 0.05$). Between the group comparison; only the M18 VAS and SF-36 pain values were found statistically significant in the positive direction in Group 2 ($p < 0.05$). ***Conclusion.*** Similar successful results were obtained in our study involving two different heating procedures up to 12 months of administering IDET treatment. But at the 18th month the 900C IDET seems to be more effective in improving the pain scores.

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Keywords: chronic low back pain, intradiscal electrothermal therapy, intradiscal treatment

Introduction

A herniated disc is caused when the nucleus pulposus (NP) breaches the annulus fibrosus (AF). Low back and leg pain, and lumbar disc disease (LDD) develop as a result of degenerative disc herniation [1]. On the other hand, 40% of chronic low back pain has been reported to be due to discogenic pain [1, 2]. Many treatment methods have been reported in the treatment of LDD, including medical (i.e., non-steroidal anti-inflammatory drugs), physical medicine and rehabilitation (PMR), and, if indicated, surgery and minimal invasive interventions (i.e., epidural therapy, intradiscal interventions) can be

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applied [1]. Currently, percutaneous modalities including intradiscal electrothermal therapy (IDET), light amplification by stimulated emission of radiation (LASER), radiofrequency (RF), and pulsed RF techniques are frequently in use [3-5].

Intradiscal electrothermal therapy was first used by Sall&Sall [6] in 1997. The standard procedure is as follows: after inserting the intradiscal catheter with the flexible tip at the posterior annulus, the tip temperature is elevated from 65^{0}C to 90^{0}C over 12.5 minutes, and the procedure is maintained at this temperature for four minutes. The temperature of AF is elevated to 60^{0}C to 65^{0}C using this procedure. The possible mechanism for IDET involves thermocoagulation of unmyelinated nerve fibers and stabilization of collagens in the annular fracture through shrinking of nociceptors [7]. Several studies have reported the short-term (12-month) and long-term (24-month) success of this treatment modality, while some others have shown no efficacy of this procedure [8-10]. On the other hand, literature reviews and meta-analyses of meticulously selected studies among patients with positive discography and magnetic resonance imaging (MRI) findings have demonstrated that the procedure can be effective and safe [10, 11]. Although rare, certain permanent or temporal neural injuries due to heat effect have been also reported following IDET as a minimal invasive procedure [12, 13].

We could not find a study comparing different catheter tip temperatures in patients who applied IDET in the literature. In this study, we aimed to evaluate the effect of IDET applied at targeted catheter tip temperatures of 75^{0}C and 90^{0}C in patients with chronic low back pain (CLBP) associated with LDD.

Methods

This study was planned as retrospective and controlled. The study protocol was approved by the local Ethics Committee (The decision number: 2011-KAEK-25 2016/08-02). A public hospital records of a total of 260 patients who were admitted to neurosurgery, algology, and PMR outpatient clinics between January 2012 and January 2015, and who underwent percutaneous intradiscal intervention were retrospectively analyzed. Inclusion criteria were as follows: the presence of low back pain unresponsive to medical or PMR therapies for more than six months, presence of a negative straight-leg raise test, normal neurological examination findings, positive discography as assessed by higher visual analogue scale (VAS) scores (> 50% with discography), absence of nerve root compression on lumbar MRI, less than 50% decrease in the disc height, and ≤ 3 mm disc protrusion with a VAS score of >5.

Exclusion criterias were as follows: extruded or sequestrated discs, two or more pathological discs, moderate or severe spinal stenosis, systemic infection, history of or current disc infection, surgical site infection, lower extremity radiculopathy, and systemic opioid use.

Fifty patients who met the inclusion criteria during follow-up were examined into two groups: Group 1 included the patients who underwent 75^{0}C IDET (n=25), and Group 2 included the patients who underwent 90^{0}C IDET (n= 25).

The level where the procedure was to be performed in the prone position was identified with C-arm fluoroscopy. After site preparation, local anesthesia was given. The needle in an appropriate length was, then, inserted 8 to 12 cm laterally in the midline at the appropriate disc level using the tunnel-vision technique. The needle site was confirmed in the anteroposterior and lateral positions. The intradiscal catheter directed with 17G (SpineCATH® NeuroTherm, Wilmington, MA, USA) was placed in the posterior annulus of the symptomatic disc. After initiating the 65^{0}C heating protocol, an increase of 1^{0}C was made within 30 seconds. Approximately five minutes after the beginning of the procedure, a stable temperature of 75^{0}C was achieved and the procedure was terminated at this temperature at 16 minutes. In Group 2, a temperature of 90^{0}C was achieved over 12.5 minutes with a standard procedure. The procedure was terminated at this temperature at 16 minutes.1 mL physiological saline + antibiotic (cefazolin) mixture was injected into the disc following the procedure. Both heating protocols were applied by the same expert investigator. The patients did not know which heating procedure they were treated. The routine controls of the patients were performed in physical therapy outpatient clinics. Before treatment (M0) and after treatment results at three (M3), six (M6), 12 (M12), and 18 months (M18) were evaluated using the VAS, Oswestry disability Index (ODI), and short form-36 (SF-36) scores by an another blind investigator who did not attempt the intradiscal electrothermal therapy in routine controls. Pain intensity was measured using 0-10 cm VAS (0 = no pain, 10 = intolerable pain) [14]. ODI is used to assess the level of functional disability. It is a self-

administered questionnaire and is consisting of 10 questions about activities of daily living scored between 0 and 5. Final result is calculated as patient's score/ maximum score X 100. The total score is between 0 and 50 [15].

The SF-36 is also a self-administered questionnaire which gives information on positive or negative health status of the individual. This scale evaluates the eight dimensions for the past four weeks [16].

The patients were asked whether they had received any other treatment when they came for control visit and were allowed to use paracetamol for pain.

Statistical Analysis

All statistical calculations were performed by using the SPSS 22.0 program. When the study data were evaluated, the Fisher Exact test was used to compare gender and the Pearson chi square ($\chi 2$) test was used in the comparison of the qualitative variables, in addition to descriptive statistical methods (frequency, percentage, mean and standard deviation). Shapiro-Wilk test were used to assess for conformity to normal distribution. When normally distribution was found, student's t test was used for comparisons between groups. When variables were found non-normally distributed, Mann Whitney U test was used for comparisons between groups and Wilcoxon test was used for intragroup analysis. Friedman's test was used for multiple time point comparisons. Where significant differences have been detected, LSD and Tukey's HSD tests were used to identify the time point/s responsible for such differences. Significance level was set at p=0.05.

Results

Of 50 patients, 20 were males and 30 were females. The median age for group 1 was 58 (range: 48 to 70) years and for group 2 was 59 (range: 36 to 70) years. When the demographic characteristics of the patients are examined, there was no statistically significant difference in terms of age, gender, body mass index (BMI), duration of disease and level of the disc between the groups (p>0.05) (Table 1). Additionally, there was also no statistically significant difference between groups in M0 VAS, ODI values and SF-36 dimensions of the patients (p>0.05) (Tables 2 and 3).

When the values of M3, M6, M12 and M18 VAS and ODI subcomponents are compared with M0 values, statistically significant improvement was found in all groups according to M0 values in both groups (p<0.05) (Table 2).

Between the groups, there was no statistically significant difference in the M3, M6 and M12 VAS and SF-36 subcomponent values (p>0.05), while the M18 VAS and SF-36 pain values were found statistically significant in the positive direction in Group 2 (p<0.05). When the values of M3, M6, M12 and M18 in ODI and SF-36 values other than pain subcomponent were compared, no statistically significant difference was found between the two groups (p>0.05) (Table 3).

Three patients in Group 2 reported pain-related discomfort during the procedure, however, pain was

Table 1. Comparison of the demographic characteristics of the patients.

	Group 1 (n = 25)	**Group 2 (n = 25)**	***p****
Age (year)	58 (48-70)	59 (36-70)	0.800
Gender			
Female	14 (56%)	16 (64%)	
Male	11 (44%)	9 (36%)	0.773
Body Mass Index (kg/m^2)	29.59 ± 4.48	29.83 ± 3.63	0.691
Duration of pain (month)	13.4 ± 4.07	14.84 ± 4.96	0.335
Level of disc			
L4-L5	19 (76%)	20 (75%)	
L5-S1	6 (24%)	5 (25%)	0.735

Data are shown as mean±standard deviation, or median (min–max) or number (percent). Group 1 = 75^0C IDET (intradiscal electrothermal therapy), Group 2 = 90^0C IDET, * Comparison between groups

Table 2. Comparison of the M0 and M3, M6, M12, M18 VAS and ODI values of study and control groups.

		M0	M3	M6	M12	M18	*p***
VAS	Group 1	6 (3-9)	2 (0-6)	2 (0-5)	2 (0-3)	3 (0-7)	***< 0.001***
	Group 2	6 (5-8)	3 (0-5)	3 (0-4)	2 (0-5)	2 (0-6)	***< 0.001***
	*p**	0.563	0.402	0.128	0.439	***0.018***	
ODI	Group 1	38 (26-50)	24 (8-48)	18 (6-36)	12 (6-20)	12 (0-28)	***< 0.001***
	Group 2	40 (32-45)	24 (20-38)	19 (12-36)	10 (6-24)	10 (6-24)	***< 0.001***
	*p**	0.334	0.408	0.328	0.067	0.321	

Data are shown as median (min–max). Group 1 = 75^{0}C IDET (intradiscal electrothermal therapy), Group 2 = 90^{0}C IDET, VAS = visual analog scale, ODI = Oswestry disability index, M0 = month 0, M3 = month 3, M6 = month 6, M12 = month 12, M18 = month 18, * Comparison between groups, ** Comparison within groups (M0 between others)

not enough to warrant the termination of the procedure. None of the patients had permanent or temporal complications. No additional analgesics, PMR, or any other intervention was given to the patients during follow-up.

Discussion

In the present study, to reduce the risk of thermal injury, we applied IDET by using 2 different catheter tips (75^{0}C and 90^{0}C) and compared the results of M0, M3, M6, M12, and M18 using the VAS, ODI, and SF-36. We reported a statistically significant improvement in both groups at the end of the M12. However, we demonstrated a statistically significant improvement in the VAS and SF-36 pain scores at M18 in patients

Table 3. Comparison of the M0 and M3, M6, M12, M18 SF-36 values of study and control groups.

SF-36	M0	M3	M6	M12	M18	*p***
Physical Function						
Group 1	45 (35-55)	65 (50-80)	70 (50-80)	65 (45-80)	60 (40-75)	***< 0.001***
Group 2	45 (35-60)	60 (45-75)	60 (45-75)	60 (45-75)	60 (45-80)	***< 0.001***
*p**	0.334	0.150	0.063	0.145	0.353	
Physical Role						
Group 1	25 (10-50)	40 (25-55)	50 (25-75)	37.5 (12.5-55)	37.5 (12.5-60)	***< 0.001***
Group 2	25 (12.5-37.5)	50 (25-75)	50 (25-75)	37.5 (12.5-60)	37.5 (12.5-60)	***< 0.001***
*p**	0.975	0.068	0.322	0.387	0.730	
Pain						
Group 1	35 (22.5-55)	62 (50-70)	55 (35-81)	45(35-81)	67(22.5-70)	***< 0.001***
Group 2	22.5 (16.30-70)	55 (22.5-70)	67 (22.5-70)	35 (22.5-70)	45 (22-70)	***< 0.001***
*p**	0.175	0.421	0.155	0.095	***0.003***	
General Health						
Group 1	35 (20-55)	65 (50-70)	60 (40-70)	60 (40-70)	50 (35-70)	***< 0.001***
Group 2	22.5 (16.30-70)	60 (35-70)	65 (40-70)	60 (35-70)	60 (35-70)	***< 0.001***
*p**	0.175	0.155	0.441	0.858	0.353	
Vitality						
Group 1	35 (25-55)	60 (25-80)	60 (50-80)	65 (25-80)	55 (50-75)	***< 0.001***
Group 2	35 (25-60)	60 (50-75)	60 (50-75)	65 (50-80)	55 (25-70)	***< 0.001***
*p**	0.690	0.192	0.138	0.707	0.920	
Social Function						
Group 1	37.5 (25-62.5)	62.5 (25-75)	62.5 (25-75)	62.5 (25-75)	62.5 (25-75)	***< 0.001***
Group 2	37.5 (25-50)	50 (25-75)	62.5 (25-75)	50 (25-75)	50 (25-75)	***< 0.001***
*p**	0.908	0.309	0.992	0.385	0.056	
Emotional Role						
Group 1	33 (16.3-50)	50 (16.3-75)	50 (16.3-75)	50 (16,3-50)	50 (16.3-50)	***< 0.001***
Group 2	33 (16.3-50)	33 (16.3-50)	33 (16.3-50)	50 (16.3-75)	50 (16.3-50)	***< 0.001***
*p**	0.418	0.567	0.406	0.791	0.837	
Mental Health						
Group 1	44 (25-55)	62 (52-71)	62 (52-71)	62 (52-71)	55 (52-80)	***< 0.001***
Group2	35 (25-52)	60 (35-80)	60 (40-80)	55 (35-80)	60 (52-75)	***< 0.001***
*p**	0.141	0.487	0.852	0.531	0.611	

Data are shown as median (min–max). Group 1 = 75^{0}C IDET (intradiscal electrothermal therapy), Group 2 = 90^{0}C IDET, SF-36 = short form 36, M0 = month 0, M3 = month 3, M6 = month 6, M12 = month 12, M18 = month 18, * Comparison between groups, ** Comparison within groups (M0 between others)

who were exposed to 90^{0}C, compared to those who were exposed to heat temperature of 75^{0}C.

With the increased use of IDET in patients with CLBP, increased complication rates have been reported in the literature. Manchikanti *et al.* [17] evaluated complications of 3,500 patients and reported that complications were often associated with technical problems and with heat. Complications associated with heat are cauda equina syndrome due to nerve injury, temporary or permanent long-term low back and leg pain, and vertebral osteonecrosis [17]. The results of this study showed that, unlike seen with the spinal cord, nerve roots and dorsal ganglion were not found in the cerebrospinal fluid (CSF); hence, they were not protected from heat temperatures of more than 45^{0}C. A meta-analysis analyzing 17 IDET studies demonstrated that this treatment modality was relatively effective and safe with a complication rate of 0.8% (0.2 to 1.4%) [11]. The insertion of a catheter is also critical in terms of the risk of complications. Konno *et al.* [18] demonstrated that 70^{0}C exposure for five minutes was sufficient to create nerve damage and that there was a possibility of injury, when the catheter was wrongly inserted. In our study, we did not encounter any complications in both groups. This may be due to the fact that our patient count was low or we did not displace the catheter wrongly.

Furthermore, human cadaver studies have investigated the mechanism of the effect of IDET and evaluated its effect on the disc and surrounding tissues [19-21]. In the studies conducted by Wegener *et al.* [19] in 10 human L4-L5 cadaver vertebral discs, discs with bulging and fissure were excluded. During the measurements of IDET treatment administered to the discs which were considered healthy, the annulus temperature was measured to be 45^{0}C, although the posterior annulus acted as a heat barrier, and a possibility of thermal injury was considered. However, one of the two risks of the study was the inability of proper insertion of the catheter; the second was the possibility of different heat distributions and variability on damaged discs involved in the study [19]. In another study, heat temperature surrounding the catheter was evaluated and a temperature of 60^{0}C to 650C was obtained, when the catheter was localized at a distance of 2 mm, whereas a temperature of 45^{0}C was reported for a distance of 9 to 14 mm [20]. Kleinstueck *et al.* [21] including 12 human cadaver specimens demonstrated that a catheter placed at a distance of 1 to 2 mm could yield collagenous denaturation and reported that the success of treatment could be attributed to other causes. On the other hand, the main limitations of cadaver studies include the lack of the effect of CSF flow and surrounding tissue structures of the platform used for the procedure [19-21].

In a study conducted by Derby *et al.* [22] different procedures of administering IDET were investigated to identify the duration of heating catheter tips at different temperatures during the administration of IDET. A total of 35 patients were evaluated in a treatment procedure involving one or two catheters. Although good results were reported at high temperatures in this retrospective study including 25 patients at eight months, its 16-month follow-up results revealed that the treatment was not effective at high temperatures [22]. The interesting results of our study was, however, the fact that, although the degree of benefit for VAS and SF-36 pain subgroup scores at a catheter tip temperature of 75^{0}C which decreased 12 months after treatment, we did not observe any statistically significant difference in the other measurable variables between the two groups.

Furthermore, although favorable conditions prevailed in the group which received a maximum heat temperature of 90^{0}C, the decline in benefit after 12 months of 75^{0}C heating can be attributed to the inability of adequately or permanently maintaining the posterior annulus nerve damage. The affinity of centrifugal growth of the annular nerve fibers was suggested to be due to pain, which also supports our findings [23]. In a study investigating the effect of heat on the nerve tissue, short-term exposure at heat temperatures of 40^{0}C to 45^{0}C were reported to induce certain damages; however, the damage was reported to be manageable and non-fatal [24]. The physiological effects of the exposures at these temperatures include an increased cellular metabolism, inactivation of enzymes, increased permeability, and increased blood flow [24]. Another factor during recovery was the degree of collagenous shrinking [25]. The catheter tip temperatures used in both groups of our study seem to have attained a degree of providing collagenous shrinking at the nucleus. For this reason, we think that there is no statistically significant difference between the groups in functional recovery in both groups.

The Limitations of the Study

There are some limitations to this study. Small sample size and retrospective design of the study can be regarded as the limitations.

Conclusions

Similar successful results were obtained in our study involving two different heating procedures up to 12 months of administering IDET treatment. But at the 18th month the 900C IDET seems to be more effective in improving the pain scores.

Authorship declaration

All authors listed meet the authorship criteria according to the latest guidelines of the International Committee of Medical Journal Editors, and all authors are in agreement with the manuscript.

Conflict of interest

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The incidence of musculoskeletal system occupational diseases among tuberculosis laboratory workers

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ABSTRACT

Objective. Health care workers are exposed to various kinds of professional risks like needle stick injuries, lower back and back problems, allergies, violence and stress. Health care workers in tuberculosis laboratory are exposed to both infection and musculoskeletal system occupational disease risks because of using Class II, Type B biological safety cabinets and laboratory vortex equipment. This study was carried out to determine incidence rates and causes of the musculoskeletal system occupational diseases among health care workers in tuberculosis laboratories of two State hospitals in Ankara. ***Methods.*** Study population was composed of 16 laboratory workers in tuberculosis laboratories of two State hospitals in Ankara. Data was collected using a questionnaire. ***Results.*** Thirteen (81.2%) laboratory workers were male and three (18.8%) were female. The mean age of the subjects was 40.1 ± 7.0 years and average duration of occupation of subjects was 208.3 ± 11.6 month. According to the data, of the 16 personnel, 10 (62.5%) had occupational disease. Incidence rates of occupational diseases were as follows; 62.5% shoulder pain, 25.0% wrist pain and 18.8% elbow pain. Duration of their occupation was significantly associated with elbow pain ($p = 0.037$). There was a significant relationship between hand and wrist pain and smoking ($p = 0.042$). Seventy-five per cent of laboratory workers did not think they had enough information on occupational diseases, and 68.8% of them wanted to have information about occupational diseases. ***Conclusions*** The most prevalent occupational diseases among the tuberculosis laboratory workers in our sample were shoulder, elbow and wrist pains. Duration of occupation and smoking were associated with the incidence of occupational diseases.

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Keywords: Tuberculosis laboratory, musculoskeletal system, occupational diseases

Introduction

Musculoskeletal system diseases (MSDs) are "work-related" diseases or conditions in muscle-skeletal system as described by International Occupational Health and Safety Committee. "Work-related" term has been used by World Health Organization for describing scientific cause of a

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multifactor condition arising from the effect of two factors such as performing a work and working environment. MSDs develop as a result of repetitive motions such as twisting, stretching, gripping, holding, pressing and reaching, which lead to damage in tendons, muscles, nerves and other soft tissues [1]. Occupational disease-related MSDs arise as a result of damaging effect of repetitive physical motions on tendons, muscles, nerves and other soft tissues. The main complaint is pain in upper extremities, neck, shoulder, hand wrists and lower back. Etiological factors are bad postures and motions, excess load on muscles during work, speed, duration and repetitive characters of work, excess labor during motion, vibration, heat and use of tools with poor ergonomics. Thirty five million health workers worldwide constitute 12% of all working population [2]. Job accidents and occupational diseases are among the major problems of working life. According to work safety studies, 98% of work accidents are preventable. For the prevention of occupational diseases and job accidents, continuous health checks have been introduced for workers [3]. MSDs are common among health workers. It has been reported that MSDs have considerable effects on life quality, reduce working life, increase work limitation and necessitate changing the work of individual. It could lead to economic problems for individual and for society at large. A study revealed that MSDs affect lower back region most in health workers [4]. Incidence of the condition in upper extremity has been reported to be 16.2% for wrists/hands, 12.6% for shoulder and 7.1% for elbow. In addition to occupational risks exposed by workers in other sectors, health workers are subject to some extra risks unique to their work. These additional risk factors show a wide spectrum involving needle stick injuries, back and lower back problems, latex allergy, violence and stress. Hospital laboratories involve many hazards for health workers. Biological hazards are leading ones due to working with highly concentrated pathogens.

Tuberculosis laboratory is known as dangerous laboratory group and the primary aim of tuberculosis laboratories is to detect infectious pulmonary tuberculosis cases, to follow-up treatment and post-treatment patients. Tuberculosis laboratory is required to have at least one biosafety cabinets for culture and drug sensitivity studied. In addition to personal protective equipment, aerosol-forming processes (pipetting, vortexing, mixing, agitation, transferring) must be done in biosafety cabinets and specially designed centrifuges should be used for centrifugation. Biological analysis laboratories such as a tuberculosis laboratory have health concerns due to presence of chemicals and medical apparatus and to ergonomic problems (inappropriate postures, heavy loads) in addition to concerns arising from pathogens. Biosafety cabins in the tuberculosis laboratory often cause musculoskeletal disorders.

Tuberculosis laboratory workers are exposed not only to bacteriological risks but also to MSDs. In the literature, there are not enough studies about this subject in tuberculosis laboratory workers. In the present study, MSDs, frequently diagnosed in workers of tuberculosis laboratories but rarely considered as occupational disease, and their reasons were studied.

Methods

Formal request was made to Public Health Laboratories of Ankara Public Health Directorate and in tuberculosis laboratory of Atatürk Training and Research Hospital for Chest Diseases and Surgery for visits to departments before the study, and permission was granted. Tuberculosis laboratory workers to participate in the study were informed in advance and interviews were made with ones willing to participate. Sixteen laboratory technicians working in tuberculosis laboratory constituted the study population. No sampling was made and all sixteen workers comprising the whole population was studied. Data were collected by a single investigator through face-to-face interviews and observation techniques. Data collection tool / questionnaire form of the study was conducted on a total of tuberculosis laboratory workers in order to determine what they know about MSDs.

Duty of a technician working in a tuberculosis laboratory is to search for the presence of Mycobacterium tuberculosis bacillus in material (pleura, sputum, tissue, urine, feces, etc.) sent to laboratory. In tuberculosis laboratory, following procedures are applied for each materials in Class II, Type B biological safety cabinet (air flow is from the room where user is located towards inside the cabinet so that user safety is ensured): a certain amount of sodium hydroxide is added into each material coming to laboratory in a container with a special lid and then lid is closed. Fifteen minutes later, material is mixed using vortex machine (a tool used for mixing laboratory tubes) for 1-2 minutes, buffer solution is added to adjust pH and the tube is centrifuged for 15

Figure 1. Working images of health personnel in tuberculosis laboratory by Class II, Type B safety cabinet and vortex machine.

minutes. Then materials are inoculated in Lowenstein Jensen medium and stained. All these processes are conducted by laboratory worker holding material with his/her hands and raising arms about shoulder level (Figure 1).

Questionnaire forms including questions categorized in six main groups about what MSDs which especially due to vibration, repetitive motion and poor posture disturbance are and what they should be careful about were directed to health workers and were completed by face-to-face method. Questionnaire technique was used in which cross-sectional and descriptive questionnaire was employed to collect data for the study. Based on the information in literature, questionnaire forms having 15 questions were prepared. Tuberculosis laboratory employees were asked questions about musculoskeletal disorders which especially due to vibration, repetitive motion and poor posture disturbance. The form contained questions about variables such as age, gender, marital status, clinic in which the technician was employed, duration and type of work, smoking, pain character in the upper extremity area, medical treatment status as well as questions measuring the level of information about MSDs as occupational disease. Information was gathered from participants about whether they were hospitalized due to upper extremity complaints, whether they changed their works, whether they experienced pain in last week, month or year, whether the pain affect their work/family life, whether they visited a physician/physiotherapist, whether they used pain killers and whether they underwent an operation because of these complaints. The relationship between the duration of work and MSDs was investigated.

Statistical Analysis

Data were analyzed as frequency and percentage distribution using SPSS 18.0 statistical analysis software. Pearson Chi-Square, Fisher's Exact Test, Kruskal Wallis Test, Continuity Correction Test and Mann-Whitney U Test were used in analyses. Two sided p value was used in all analyses and $p < 0.05$ was considered significant.

Table 1. Demographic data of laboratory workers.

No.	Gender	Marital status	Duration of work (month)	Smoking	Shoulder pain	Elbow pain	Hand /hand wrist pain	Medical treatment
1	F	Married	120	Never	No	No	No	No
2	F	Married	252	Gave up	No	No	No	No
3	F	Married	352	Gave up	Yes	Yes	Yes	Medicine
4	F	Single	240	Smoking	Yes	No	Yes	No
5	M	Single	73	Never	No	No	No	No
6	M	Single	300	Smoking	Yes	No	No	No
7	F	Married	288	Never	Yes	No	No	Physiotherapy and medicine
8	F	Married	249	Gave up	Yes	No	No	No
9	F	Married	278	Never	Yes	No	No	No
10	F	Single	312	Gave up	Yes	Yes	Yes	Physiotherapy and medicine
11	F	Married	30	Never	Yes	No	No	No
12	F	Married	22	Smoking	Yes	No	No	No
13	F	Married	36	Never	No	No	No	No
14	F	Married	264	Smoking	Yes	Yes	Yes	Physiotherapy and medicine
15	M	Single	278	Never	No	No	No	No
16	F	Single	240	Smoking	No	No	No	No

F = female, M = male

Results

Thirteen (81.2%) of the 16 tuberculosis laboratory workers were women and three (18.8%) were men. Average age was 40.1 ± 7.0 years and average duration of occupation was 208.3 ± 11.6 months. In terms of smoking, nine workers (56.25%) never smoked and seven (43.7%) were actually smoking or had smoked in the past and gave up. Demographic data about participants were given in Table 1.

Results showed that 10 out of 16 workers (62.5%) had MSDs. Occupational diseases detected among tuberculosis laboratories were shoulder pain (62.50%), hand wrist pain (25.00%) and elbow pain (18.75%) (Figure 2). There was a significant correlation between the duration in occupation and elbow pain ($p = 0.037$) (Figure 3.). Another significant correlation was found between smoking and elbow pain ($p = 0.049$) (Figure 4).

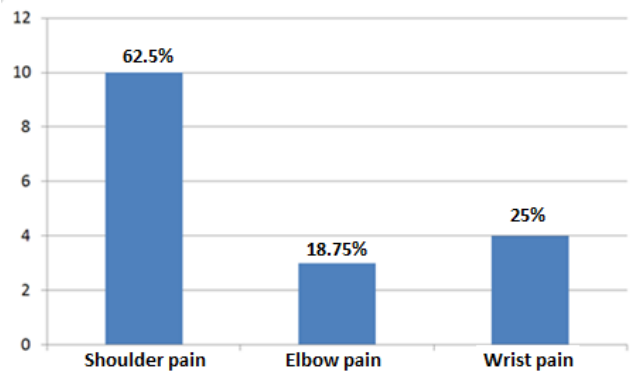

Figure 2. Incidence rate of musculoskeletal system diseases.

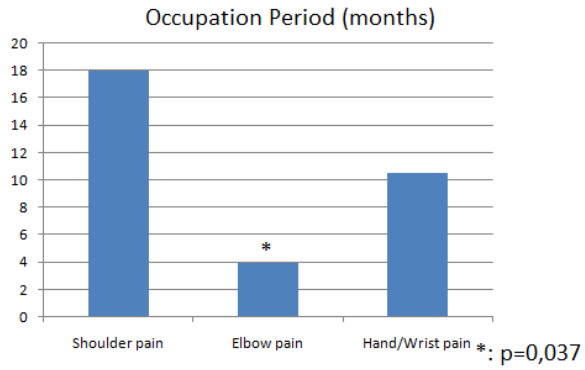

Figure 3. Relationship between duration of work and musculoskeletal system diseases among laboratory workers.

One person diagnosed with MSDs was treated with drug treatment (6.25%) and three with drug treatment plus physiotherapy (18.75%). No laboratory worker had history of surgery due to MSDs.

Figure 4. Relationship between smoking and musculoskeletal system diseases among laboratory workers.

Seventy-five of the laboratory workers considered themselves lacking sufficient amount of knowledge about occupational disease (Figure 5). Of all laboratory workers, 68.8% wanted to have detailed information about MSDs (Figure 6).

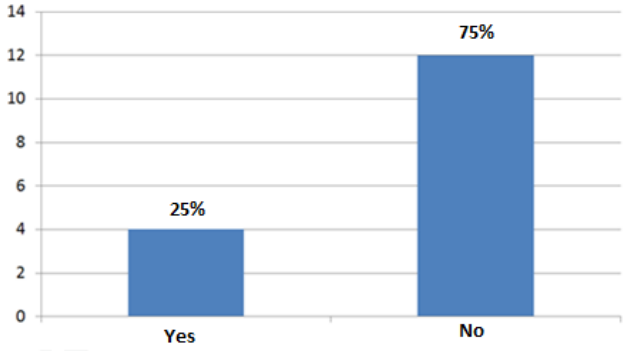

Figure 5. Percentage of laboratory workers who considered themselves informed enough about occupational diseases.

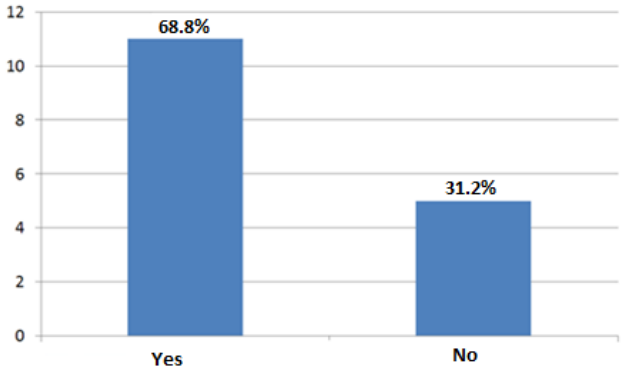

Figure 6. Percentage of laboratory workers who wanted to get detailed information about occupational diseases.

Discussion

MSDs are among the most significant problems of working life [5]. MSDs involve muscles, tendons,

ligaments, joints, peripheral nerves and blood vessels, and could lead to inflammatory and degenerative conditions causing pain in the involved area [6]. MSDs-related risk factors are physical, social and personal [7]. Main complaint is pain in upper extremities, neck, shoulder, hand wrists and lower back [8]. In our study, tuberculosis laboratory workers were found to have upper extremity-related diseases than other extremity-related diseases.

MSDs could have potential adverse impacts on both individuals and institutions. Its relationship with physical and mental health of work force has been studied in various investigations. In a study conducted on 410 office workers, reported musculoskeletal impairment incidence in the upper extremities was 27.5%, followed by impairment in shoulder (18.1%), hand/hand wrist symptom (13.9%) and impairment in elbow (5.3%) [9]. A study carried out on nurses revealed that 69% of the nurses suffered from back pain, 46% from shoulder pain, 54% from neck pain and these complaints were shown to be related to working area [10]. In the present study, 62.5% of health personnel working in tuberculosis laboratory had shoulder pain, 25.0% had hand wrist pain and 18.75% had elbow pain.

Health workers have risk for MSDs. Especially nurses rank third after heavy industry workers and heavy vehicle drivers to suffer from back pain due to their occupation. Health workers other than nurses such as dentists, physiotherapists and caregivers also have high risk for back pain. Smith *et al.* [11] have reported that musculoskeletal system pains are most common in shoulder, waist, neck and lower back regions in Japanese nurses. It was determined in the present study that laboratory workers had higher rates of upper extremity diseases because of having to work with Class II, Type B Biosafety cabinets.

There are mechanical risks in tuberculosis laboratory because of use of machines, laboratory tools and pressure containers such as autoclave. Centrifuges are machines working by high-speed spinning and could cause problems due to chemicals and wearing of metal over time. Mounting centrifuges on uneven surfaces could lead to vibration and falling. Working in a narrow area could cause a hot and noisy working environment. Our literature survey showed that MSDs were studied among health workers, specifically in nurses; however, there was no report in literature on MSDs among tuberculosis laboratory workers to our best knowledge [9, 10]. Workers in tuberculosis laboratories were exposed to risks that could lead to MSDs by working in Class II, Type B biosafety cabinets, in microscope studies, during separation of specimen on counters and working with monitors. We found that the risk of getting MSDs was high when working in the Type B biosafety cabinet. Works requiring repetitive motions are tiring for employees. Health workers cannot entirely relax during the short breaks between duties. Although repetitive motions demand minimum power, efforts needed to continue these motions over time increase regularly. When the activity is continued without break despite the accumulated fatigue [12]. Workers exposed to vibration may have complaints about weakness and pain in hands and arms. Muscle fatigue could lead to injuries in some people. Since the health problems due to vibration, an inevitable fact of working life, arenotevident right after the start of exposure, vibration is not considered as a dangerous risk factor [13]. In our study, tuberculosis laboratory workers were found to have excessive fatigue, depression and loss of work power. Hand/hand wrist pain due to use of vortex machine has been frequent among the subjects of the present study. In addition, a positive association was found between smoking and hand/hand wrist pain.

There are some difficulties in recording occupational diseases in Turkey. Since background for the conditions of occupational diseases are difficult to determine, they may sometimes go unnoticed. A occupational disease can be apparent only after a long incubation period and lead to permanent damage. Despite their high incidence rates, MSDs are rarely reported as occupational diseases. Total number of reported cases of occupational diseases in Ankara Province was 6 in 2013, 9 in 2014 and 46 in 2015. According to 2016 hospital admission data of Gaziosmanpaşa University, Health, Research and Practice Hospital, 104 patients (44 male, 60 female; average age 56.6±11.7) had frozen shoulder, rotator cuff tendon injury and shoulder lesion diagnoses, but no patient had these diagnoses as occupational disease. Similarly, despite the presence of MSD diagnoses among tuberculosis laboratory health personnel, they were not reported as occupational disease.

The most important aspect of occupational diseases is that they are 100% preventable. When checking methods are appropriately used and necessary risk management practices are implemented, occupational diseases could be eliminated in businesses.

The Limitations of the Study

Study population was small because only tuberculosis laboratory workers were included. Since this was a questionnaire study, MSD diagnoses were not supported by laboratory tests and physical examination other than major and minor findings. Therefore, other pathologies that could not be excluded only by anamnesis should also be considered.

Conclusions

In conclusion, it should be kept in mind that MSDs could appear as occupational diseases among tuberculosis laboratory workers. It is thought that improved physical working conditions, orderly implementation of periodic health checks and administering appropriate treatment to workers who had diagnosis for occupational diseases could lower the negative effects of MSDs due to occupational exposure. In addition, it could be useful to organize physical exercise programs to strengthen body muscles such as waist, shoulder and neck muscles for all health workers and to teach them working in appropriate posture to eliminate and prevent MSDs.

Authorship declaration

All authors listed meet the authorship criteria according to the latest guidelines of the International Committee of Medical Journal Editors, and all authors are in agreement with the manuscript.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Surgical interventions for autogenous arteriovenous fistula aneurysms in hemodialysis patients

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ABSTRACT

Objectives. The aim of this study was to emphasize the importance of surgical intervention perfotmed before development of arteriovenous fistula (AVF) aneurysm complications. ***Methods.*** The patients were categorized into two groups: Patients undergoing elective surgery for autogenous AVF aneurysm were defined as elective group (Group 1), whereas those who underwent emergency surgery due to ruptured aneurysmal fistulas were defined as emergency group (Group 2). All elective cases were evaluated by doppler ultrasonography before surgery. All patients had temporary hemodialysis catheters. In the patients with salvaged fistulas, the fistulas was rested for 1 week. A new fistula was created in patients with not salvaged fistula. ***Results.*** A total of 31 patients (54.8% male, mean age: 41.2 ± 14.7 years) were in Group 1 and 7 patients (57.1% male, mean age: 53 ± 9.4 years) were in Group 2. Significant difference was observed between two groups in terms of fistula preservation. Salvaged fistulas were significantly higher in the Group 1 than Group 2 ($p = 0.003$). In Kaplan-Meier curves, cumulative primary AVF patency rates at 1, 3 and 6 months were 96.3%, 81.5%, and 77.8% in Group 1 and 66.7%, 66.7%, and 66.7% in Group 2, respectively (log-rank; $p = 0.536$). ***Conclusions.*** Consultation of these cases with a cardiovascular surgeon before they reach the rupture stage is an important condition for both the patency of the fistula and the vital risk of the patient.

Eur Res J 2018;4(3):180-186

Keywords: Arteriovenous fistula aneurysms, salvage treatment, hemodialysis

Introduction

Haemodialysis via an autogenous arteriovenous fistula (AVF) is the most frequently used treatment for end-stage renal failure worldwide [1]. Development of aneurysmal dilatation of the AVF is an important complication which occurs in 5-6% of the cases and has a significant risk of rupture [2]. Aneurysms are associated with multiple complications that increase the risk of life-threatening fistula bleeding, fistula loss, and even patient death [3]. In addition, aneurysms can cause tissue necrosis and erosion and local infection.

Pseudo-aneurysms can be caused by anastomotic leakage or may occur later as a complication of infection. However, true AVF aneurysms are occurs as a result of repeated intervention for vascular access to

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multiple small fibrous scars in the vessel wall, which may expand over time and may result in localized aneurysmal regions. Aneurysmal dilation also may occur in non-needled areas and the highflow though the vessel can cause in abnormal shear stress, which promotes outward remodeling and gradual dilation with grossly increased calibre of the vessel [4].

The aim of this study was to emphasize the importance of intervention performed before development of AVF aneurysm complications.

Methods

Patients

This retrospective observational study includes patients with end-stage renal failure who underwent surgery due to autogenous AVF aneurysms between 2014 and 2018 at Department of Cardiovascular Surgery, Bursa Yüksek İhtisas Training and Research Hospital,Turkey. The study was approved by institutional review committee.

All data retrieved from the hospital's medical files analyzed retrospectively. All data were recorded as age, gender, comorbidities (Hypertension, diabetes mellitus, coronary artery disease), type of AVF and duration of AVF. The patients were categorized into two groups: Patients undergoing elective surgery for autogenous AVF aneurysm were defined as elective group (Group 1), whereas those who underwent emergency surgery due to ruptured aneurysmal fistulas were defined as emergency group (Group 2). All elective cases were evaluated by doppler ultrasonography before surgery. All patients had temporary hemodialysis catheters. In the patients with salvaged fistulas, the fistulas was rested for 1 week. A new fistula was created in patients with not salvaged fistula.

Surgery

While all emergent procedures were carried out under general anaesthesia, elective procedures were carried out under local anaesthesia accompanied with sedation. Our priority was to stop the bleeding in emergency ruptured cases. The aneurysm sac was isolated from surrounding tissue to reach to the root of the aneurysm and then to the afferent and efferent arteries (Figure 1). Aneurysmal sacs were opened, after resecting the sacs, in cases with thrombus, thrombectomy was performed. Then appropriate graft materials were interposed between related artery and the previously dissected vein or between arterialized veins. Plication was performed in the presence of the suitable aneurysmal sac (Figures 2a and 2b).

Postoperative Evaluation

Postoperative fistula evaluation was done at 1st, 3rd, and 6th months. The follow-up continued until death or no further communication was possible to the patient. In such cases, data from the last visit were used. AVF patency was assessed by physical examination for the presence of a palpable thrill. In the absence of a palpable thrill and pulse, it was evaluated as failure. When presence of a palpable

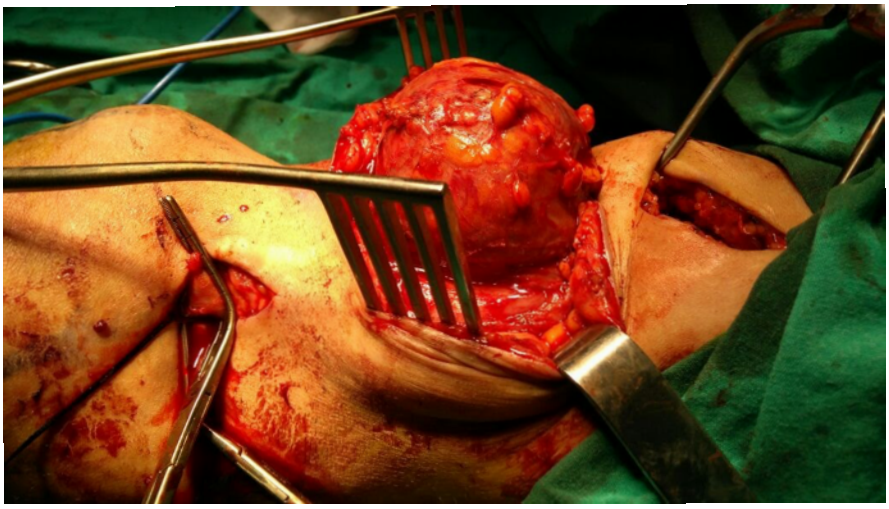


Figure 1. Aneurysm sac isolated from surrounding tissue.

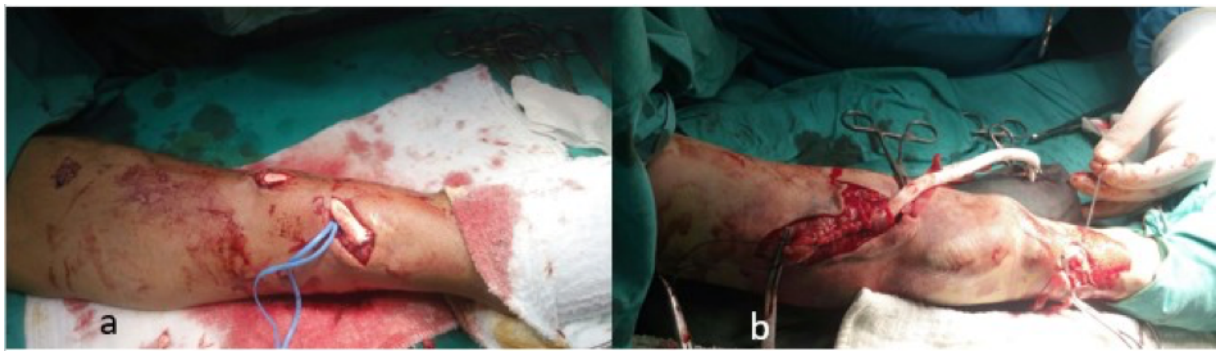


Figure 2. Graft interposition view after aneurysmectomy (a) and aneurysm plication view (b).

pulse, doppler USG was performed and blood flow measured. Those below the flow rate of 200 ml/min were considered as a failured AVF.

Statistical Analysis

Statistical analysis data were analyzed with the Statistical Package for the Social Sciences (IBM SPSS Statistic Inc. version 21.0, Chicago, IL, USA). Continuous and ordinal variables were expressed as mean ± standard deviation and nominal variables were expressed as frequency and percentage. Kolmogorov-Smirnov test and Shapiro-Wilk tests of normality were used to identify distribution of variables. Chi Square test and Fisher's Exact test were used to compare two groups for nominal variables. Student-t test was used to compare two groups for continuous variables normal distribution. Mann-Whitney U test was used to compare two groups for continuous variables without normal distribution. Long-term results were analyzed by Kaplan Meier curves, and differences in subgroups were assessed by the log-rank test. For all tests, a p value of < 0.05 was considered statistically significant.

Results

A total of 31 patients (54.8% male, mean age: 41.2 ± 14.7years) were in Group 1 and 7 patients (57.1% male, mean age: 53±9.4 years) were in Group 2. The demographic and clinical properties of the subjects are summarized in Table 1. Both groups were generally similar in regards to demographic properties. The size of aneurysm was 52.3 ± 14.5 mm in Group 1 and 68.6 ± 17.5 mm in Group 2. In terms of size of aneurysm there was statistically significant difference between two groups. ($p = 0.014$) (Table 1).

The reasons of the operations are shown in table 2 and the most common cause was skin thinning or ulceration (81.6 %). Some of treated aneurysms have shown in Figure 3a, 3b and 3c. All of the aneurysms operated were true aneurysms.

Table 1. Demographic features of the patients

Variables	Group 1 (n = 31)	Group 2 (n = 7)	*p* value
Age (years)	41.2 ± 14.7	53 ± 9.4	0.051*
Gender, n (male %)	17 (54.8)	4 (57.1)	0.912 [#]
Hypertension, n, %	19 (61.3)	6 (85.7)	0.219 [#]
Diabetes Mellitus, n, %	16 (51.6)	2 (28.6)	0.270 [#]
History of CAD, n, %	9 (29)	2 (28.6)	0.981[#]
Type of AVF			0.728 [#]
Brachiocephalic, n, %	20 (64.5)	5 (71.4)	
Radiocephalic, n, %	11 (35.5)	2 (28.6)	
Size of Aneurysm (mm) (min-max)	52.3 ± 14.5 (35-100)	68.6 ± 17.5 (45-100)	**0.014**[b]
Duration of AVF (years)	6 ± 2.6	7.9 ± 2.5	0.102*

Group 1= elective surgery, Group 2 = emergent surgery, CAD = Coronary Artery Disease, AVF = Arteriovenous Fistula, [#] Pearson Chi- Square, *Student's *t* test, [b] Mann Whitney Test

Table2. Indications of aneurysm for treatment

Causes of Surgery	**n = 38**
Skin thinning or ulceration, n (%)	31 (81.6)
Expanded aneurysm, n (%)	27 (71.1)
Rupture, n (%)	7 (18.4)
Pain with aneurysm, n (%)	4 (10.5)
Failure with thrombosis, n (%)	5 (13.2)

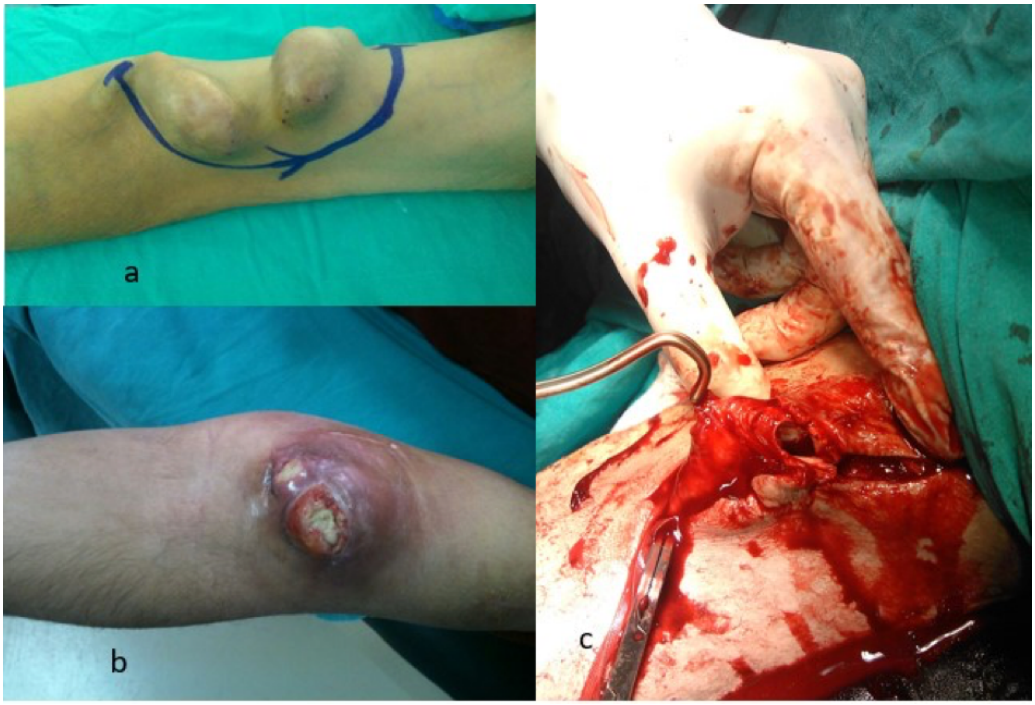


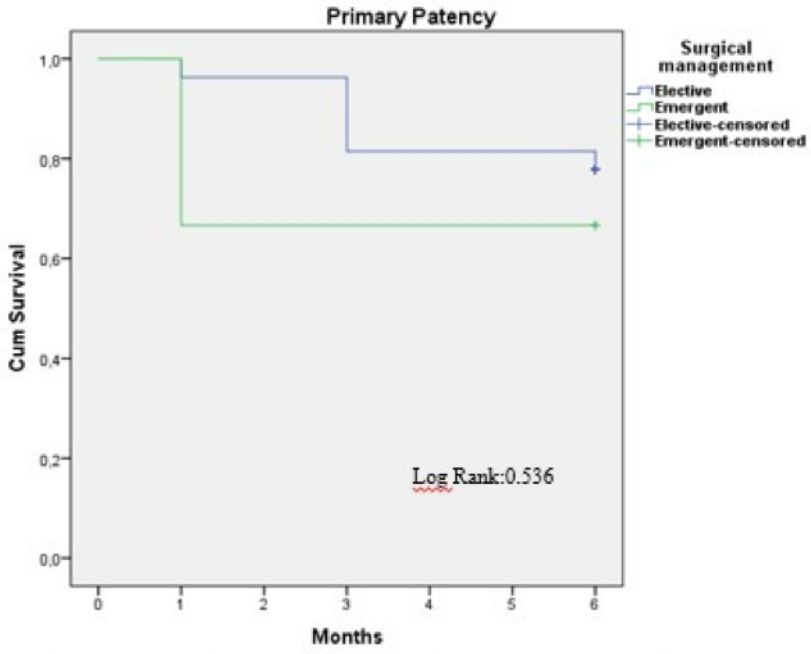
Figure 3. AVF aneurysm (a), AVF aneursym with skin thinning and ulceration (b), and ruptured AVF aneurysm (c).

The comparison of post-intervention fistulas status are shown in Table 3. Significant difference was observed between two groups in terms of fistula preservation. Salvaged fistulas were significantly higher in the Group 1 than Group (p = 0.003 [Pearson Chi-Square] and p = 0.013 [Fisher's Exact Test]) (Table 3). There was worse fistula rescue in Group 2. A total of 31 (81.6%) fistulas were salvaged. Three

Table 3. Post-intervention fistulas status

	Group 1 (n = 31)	**Group 2 (n = 7)**	***p value***
Salvaged AVF, n, %	28 (90.3)	3 (42.9)	[#] **0.003**
			[a] **0.013**
Not Salvaged AVF, n, %	3 (9.7)	4 (57.1)	[#] **0.003**
			[a] **0.013**

[#] Pearson Chi- Square, [a] Fisher's Exact Test, AVF = Arteriovenous Fistula



	Months	1	3	6
Salvaged AVF	N. at risk	27	23	19
	SE	0,036	0,075	0,080
	Patency rate	96.3 %	81.5 %	77.8 %
Not Salvaged AVF	N. at risk	2	2	2
	SE	0,272	0,272	0,272
	Patency rate	66.7 %	66.7 %	66.7 %

Figure 4. Kaplan-Meier curves; cumulative primary patency rates for six months.

fistulas in the elective group could not salvaged due to axillary or subclavian vein thrombosis. In twenty-five (80.6%) cases we performed aneurysm excision and repair with graft interposition. Aneurysm plication was applied to others.

The 6-month follow-up was completed in all patients. In Kaplan-Meier curves, cumulative primary AVF patency rates at 1, 3 and 6 months were 96.3%, 81.5%, and 77.8% in Group 1 and 66.7%, 66.7%, and 66.7% in Group 2, respectively (log-rank; $p = 0.536$) (Figure 4). In total, 7 (22.6%) AVF failure observed in the follow-up period.

Discussion

For patients with renal insufficiency, hemodialysis is an inevitable lifelong requirement until the renal transplant, and deprivation of the patient's vascular access pathway can be life-threatening. Many late complications, such as thrombosis, venous hypertension, aneurysm formation, hemorrhage, vascular steal syndrome, stenosis, and heart failure may occur following arteriovenous fistula surgery [5]. The treatment of the fistula complications should treat the problem and maintain the fistula function. In this study, we analyse the follow ups and the results of AVFs that we intervened due to aneurysm formation. In our study, we determined the preservation rate of the AVFs as 90.3% in electively operated group and as 42.9% in emergency operated group due to rupture ($p = 0.003$) (Table 3).

When aneurysm and tortuosity occur in AVF, cannulation may become difficult and flow might be unreachable due to thrombus formation in the aneurysm. Other sequelae of aneurysm's degeneration is corruption of the overlying skin that associated with risks of bleeding and infection [6]. In our study, as in other studies, skin thinning and ulceration were the most common reason for surgical intervention [7-10]. Cutaneous atrophy may lead to ulceration and associated catastrophic haemorrhage which requiring emergency ligation of the fistula [11]. By the reason of life threatening bleeding due to rupture, we had to ligature 4 (57.1%) of the fistulas that we had performed emergency surgery. But this rate remained

at 9.7% in elective cases and we saved 90.3% of the fistulas. In literature, we could not find fistula salvage rates in surgery for ruptured AVF compare with non-ruptured AVF aneurysms. In some of them, fistula preservation rates were given as 95% [12] and 88% [13] but elective and emergency surgery situation were not discriminated. For this reason, we think that our study will be useful for the literature. During skin thinning or ulceration stage AVF aneurysms is more inclined to bleeding. Rupture may become inevitable if this situation accompanied by an increase in the size of the aneurysm. In our study, the size of AVF aneurysms (68.6 ± 17.5 mm) which operated due to rupture was large as statistically significant ($p = 0.014$) (Table 1). NKF-DOQI guidelines state that intervention on a fistula should be performed in the presence of aneurysm formation and the aneurysmal segment should not be cannulated [3]. The treatment of focal fistula aneurysms has traditionally include resection of the aneurysm materials and interpositioning bypass by using prosthetic graft. Previously reported techniques for treatment of AFV pseudoaneurysms and aneurysms have included the use of self-expanding stent grafts [14], prosthetic graft exoprosthesis reinforcement [8], use of Tubularized CorMatrix [15], aneurysmorrhaphy [12], and partial aneurysmectomy with native reconstruction [9, 16] or prosthetic interposition [17]. Patel *et al*. [18], reported that they performed resection of the aneurysm, followed with graft interpositioning or primary repair and no fistulas were compromised or lost as a result of the procedure. Georgiadis *et al*. [19], in a study which they performed aneursym excision and graft interposition with PTFE graft, reported that patency rates of the repaired AVF as nearly 70%. Patency ratios of different techniques have been reported in previous studies. In our study, we performed aneurysm excision and repair with graft interposition in 25 (80.6%) patients and applied aneurysm plication in 6 (19.4%) patients. Cumulative primary AVF patency rates of our procedures was 77.8 %. Our patency rates are similar to the literature.

In this study, we focused on the management of AVF aneurysms.AVF aneurysm is definitely a condition to be treated. There are many surgical procedures and approaches in the literature. In all of these applications, it is important to ensure the patency of AVF. Timing of intervention is the most important point to maintaining the continuity of the fistula, according to us. Because, as we have seen, fistula rescue rates in ruptured AVF aneurysms are obviously less than in elective surgery. As a result of our study, we think that AVF preservation is at the second plan in the presence of life threatening bleeding in an aneurysm rupture.

Conclusions

In conclusion, consultation of these cases with a cardiovascular surgeon before they reach the rupture stage is an important condition for both the patency of the fistula and the vital risk of the patient. It is important to educate the hemodialysis team about fistula use and follow-up. Especially it should be explained that venous punctures applied to the same region may cause serious complications in the future and early surgical treatment may protect the fistula. This tells us that the surgeon, nephrologist and dialysis nurse should be in cooperate.

Informed consent

Written informed consent was obtained from the patients for publication of images.

Author Contributions

Consept-Design: KKÖ, USS; Data collection: NK, KKÖ, FT; Analysis: KKÖ, FT; Literature search: KKÖ, NK; Writing: KKÖ, USS, ŞY; Critical review: ŞY.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Can decrease in hand grip strength in carpal tunnel syndrome be explained by interosseous muscle and intermetacarpal space dimensions?

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ABSTRACT

Objectives. To investigate the correlation of the grip strength with sonographic measurement of interosseous muscle (IOM) and intermetacarpal space (IMS) of the hands in carpal tunnel syndrome (CTS) patients. ***Methods.*** A total of 96 hands of 48 female patients constituted the study group. Of those, 36 hands of 18 patients (mean age: 50.2 ± 9 years) had CTS confirmed by electro-diagnostic tests. Sixty hands of 30 healthy volunteers (mean age: 45.2 ± 9.7 years) constituted the control group. Grip strength was assessed by Jamar hand dynamometer. IOM and IMS dimensions for all hands were measured sonographically at three levels (2nd, 3rd and 4th intermetacarpal; palmar side for IMS, dorsal side for IOM) by the same radiologist. Spearman and Mann Whitney U tests were used for statistical analysis. ***Results.*** The median hand grip strength was determined as 11.3 kg (min-max = 7.2-18.1 kg) in the CTS group and 19.5 kg (min-max = 7.8-30.5 kg) in the control group, with a statistical difference between the two groups ($p < 0.03$). In both groups, there was a positive correlation between the IOM-IMS dimensions and grip strength ($p < 0.05$). Sonographically, IOM-IMS measurements in CTS group were significantly lower than control group ($p < 0.01$). ***Conclusion.*** To our knowledge, this is the first study evaluating the correlation of grip strength and the sonographic IOM-IMS measurements in CTS patients. The muscular atrophy, which is generally a finding of advanced disease, may be revealed by sonographical measurements earlier than the physical examination findings.

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Keywords: hand grip strength, carpal tunnel syndrome, interosseous muscle, intermetacarpal space dimensions, ultrasound

Introduction

Carpal tunnel syndrome (CTS) is an entrapment neuropathy that causes impairment and decrease in hand grip strength as well as paresthesia, which is more frequent at nights, and malfunction in the hand [1].

The thenar- hypothenar muscle groups and interosseous muscle (IOM) and lumbrical muscle groups together form the intrinsic muscles of the hand.

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IOM groups are divided into ventral and dorsal parts. There are 4 muscles on the dorsal side and 3 muscles on the ventral side. They originate from the adjacent metacarpal proximal head and attach to the base of the proximal phalanx. While dorsal IOMs abduct; ventral IOMs adduct [2, 3]. Dorsal IOMs are sonographically detectable through metacarpal interspaces from the dorsum of the hand. IOMs are observed between metacarpals as a smooth contour in a hypo-echoic structure [4]. It is known that CTS symptoms develop due to compression of the median nerve. In addition to sensory symptoms, as motor fibers are also affected, hand grip strength decreases. This is one of the most important symptoms of the disease and is associated with muscle weakness. Visible muscle atrophies are mostly located in the thenar part of the hand and are observed in advanced and severe pathology [5, 6]. Predicting muscle strength decrease with sonographically detectable parameters such as intermetacarpal space (IMS) and IOM is an important step for treatment planning in the early phase [7, 8].

Ultrasound is a useful imaging method in examining CTS. In fully developed cases, a classic triad of palmar bowing of the flexor retinaculum, distal flattening of the nerve, enlargement of the nerve proximal to the flexor retinaculum is seen. Enlargement of the nerve is stated as the most sensitive and specific criterion [9]. Hand muscle ultrasound, as being non-invasive and real-time, is a useful technique to visualize normal and pathological muscles. Neuromuscular disorders, like CTS, cause structural changes in muscles that can be visualized with ultrasound: atrophy can be objectified by measuring muscle thickness, while infiltration of fat and fibrous tissue increase muscle echo intensity [10]. The aim of this study was to examine whether decreased hand grip strength in CTS patients is associated with interosseous muscle thickness and intermetacarpal space dimensions.

Methods

The study protocol was approved by the Institutional Review Board of our hospital. The study is performed between January-August 2016. We excluded 3 patients' due to the surgery history in one hand, 2 patients are excluded because of left hand dominance and 12 patients are excluded secondarily to having diabetes mellitus.

Hence, 96 hands from 48 female participants were included in the study. All the participants were right-hand dominant, and they did not have any systemic diseases.

The patient group consisted of 36 hands of 18 participants previously diagnosed with EMG as CTS. In the physical examination, none of the patients in the CTS group had thenar atrophy. The control group was formed of 60 hands of 30 healthy volunteers and 5 hands detected as normal on EMG from the CTS patient group. For each hand, hand grip strength was measured with a Jamar dynamometer (Lafayette instrument, USA, 2004) in kilograms. To standardize the results, the hand grip strength test was conducted in the same position for each patient (shoulder in full adduction and elbow at 90°) (Figure 1).

Figure 1. Photograph showing hand grip strength measurement with Jamar dynamometer.

During the US examination, the patients were examined in a sitting position on the gurney with their hands on their knees. The fingers were spaced in the anatomical position and the dorsal and volar faces were scanned respectively (Figure 2). All patients were scanned by a radiologist with 25 years of muscle-bone sonography experience, using a B-mod US (SDU-2200; Shimadzu Corporation, Kyoto, Japan)

with an 8-10 MHz linear probe.

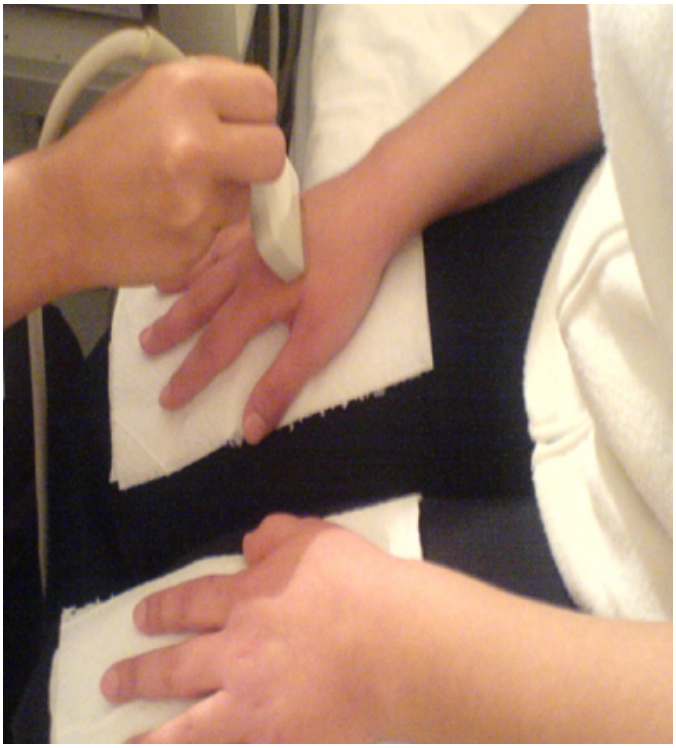

Figure 2. Photograph showing patients' position for ultrasound scan

With US, IOM groups were examined on the dorsal side in the 2nd, 3rd and 4th metacarpal spaces and the adjacent bone shaft (Figure 3). On the volar aspect, the IMSs were quantified in the 2nd, 3rd and 4th metacarpal spaces of the adjacent metacarpal distal head. On the obtained images of IMS measurements, measurements were made on the radial aspect of the lumbrical muscle planes (Figure 4). For each region, 3 vertical measurements were taken in the anteroposterior and transverse planes and the mean values for each were recorded.

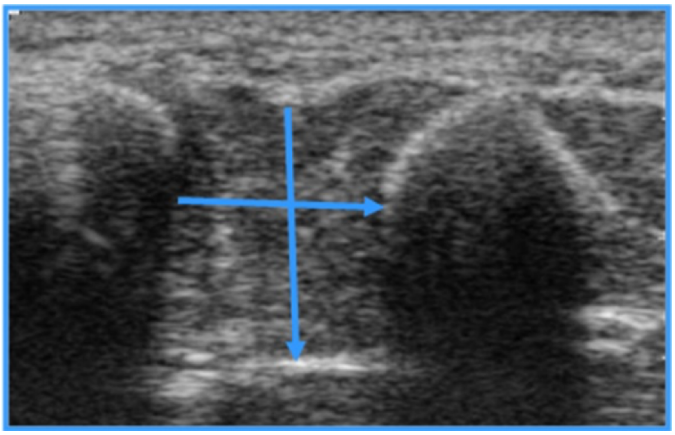

Figure 4. Intermetacarpal space, area between arrows.

To homogenize the sample, the groups were matched for age and gender, including patients with right hand dominance and excluding trauma/surgery history.

Statistical Analysis

Statistical analyses were performed using SPSS Statistics software (version 21.0; SPSS Inc., Chicago, Illinois, USA). The conformity of the data to normal distribution was evaluated with the Kolmogorov-Smirnov test. Numerical variables with normal

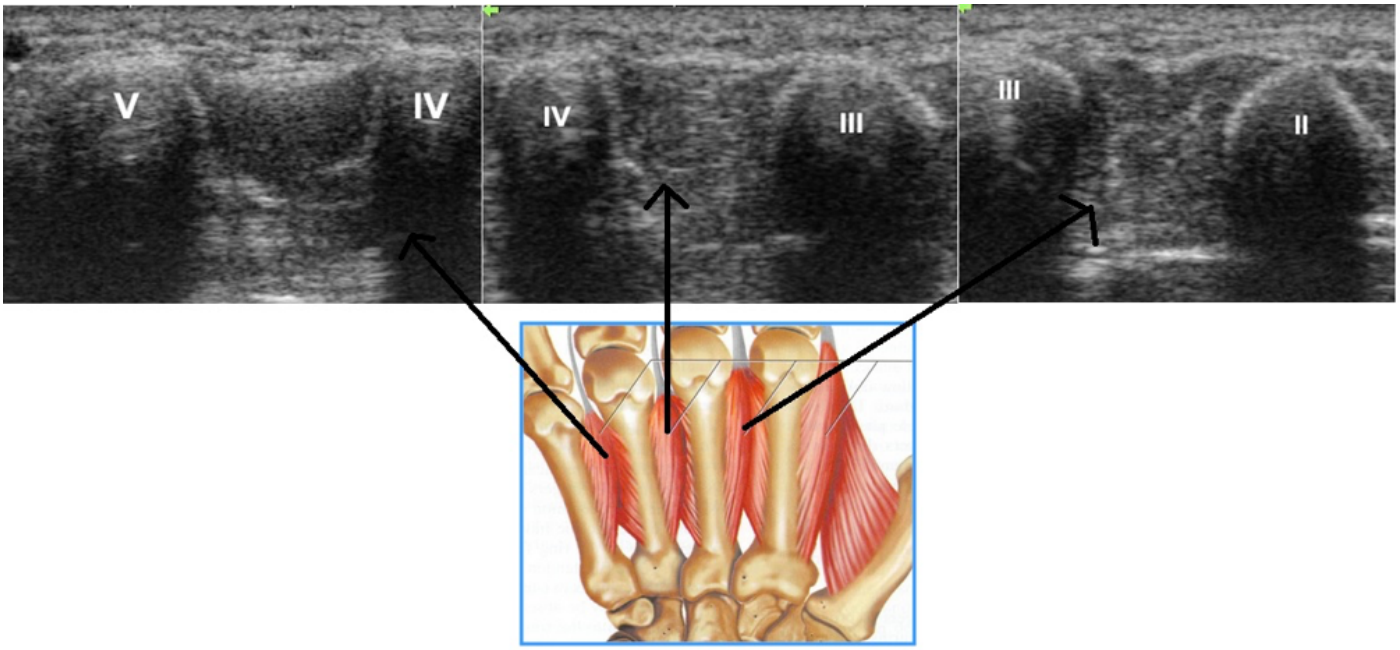

Figure 3. Sonographic pictures indicating interosseous muscle thickness measurement technique.

distribution were stated as mean ± standard deviation (SD) and those not with normal distribution were stated as median values (min.-max.). Categorical variables were shown as number (n) and percentage (%). In both groups, the relationship between hand grip and US measurements was examined with Spearman correlation analysis. To compare the CTS and control groups in terms of hand grip strength and US measurements, the Mann Whitney-U test was applied.

Results

The mean age of control group was 50.2 ± 9 years and the mean age of CTS group was 45.2 ± 9.7 years. The median hand grip strength was determined as 11.3 kg (min-max = 7.2-18.1 kg) in the CTS group, and 19.5 kg (min-max = 7.8-30.5 kg) in the control group. The IMS and IOM values for both groups are presented in Tables 1 and 2. There was a significant difference between the CTS group and the control group in terms of hand grip strength (28,103 vs. 41,005; $p < 0.01$).

In this study, the normal values for the dimensions of IMS in the anteroposterior and transverse axes were obtained. There was determined to be a correlation between these values and hand grip strength ($p<0.01$).

The IOM and IMS values of the CTS group were significantly lower than those of the control group ($p<0.01$). There was a statistically significant relationship between hand grip strength and IOM /MS values (r = 0.255-0.479, $p < 0.01$) in the control group. No such relationship was detected in the CTS group (Tables 1 and 2).

Discussion

CTS is the most frequent neuropathy of the upper limb caused by compression of the median nerve in the wrist [9]. Especially following long-term functional hand use, numbness, tingling and burning sensations are experienced in the thumb, index finger, middle finger, and radial half of the ring finger Motor symptoms such as weakness in the strength of the fingers, clumsiness and difficulty in daily life activities cause an impairment in life quality. Typically, the

Table 1. Intermetacarpal space (IMS) measurements of carpal tunnel syndrome (CTS) and control groups

IMS WIDTH	Control	CTS	*p* value
1 IMS			
Transvers	10.17 ± 1.10	10.12 ± 1.16	$p < 0.01$
Longitudinal	5.50 ± 0.70	5.45 ± 0.81	$p < 0.01$
2 IMS			
Transvers	8.62 ± 0.84	8.55 ± 1.04	$p < 0.01$
Longitudinal	5.58 ± 0.72	6.00 ± 0.92	$p < 0.01$
3 IMS			
Transvers	9.15 ± 1.16	9.05 ± 1.11	$p < 0.01$
Longitudinal	4.77 ± 0.76	4.66 ± 0.71	$p < 0.01$

Data are shown as mean ± stansard deviation. CTS = carpal tunnel syndrome, IMS = intermetacarpal spaces

Table 2. Interosseous muscles thicknesses of carpal tunnel syndrome and control groups

IOM WIDTH	Control	CTS	*p* value
2 IOM			
Transvers	9.07 ± 1.04	9.00 ± 1.06	$p < 0.01$
Longitudinal	10.28 ± 9.25	9.33 ± 1.14	$p < 0.01$
3 IOM			
Transvers	7.41 ± 0.92	7.28 ± 0.86	$p < 0.01$
Longitudinal	9.67 ± 1.51	8.95 ± 1.02	$p < 0.01$
4 IOM			
Transvers	8.37 ± 0.90	8.35 ± 0.95	$p < 0.01$
Longitudinal	9.40 ± 0.96	7.92 ± 0.84	$p < 0.01$

Data are shown as mean ± stansard deviation. CTS = carpal tunnel syndrome, IOM = interosseous muscles.

dominant hand is affected [11, 12]. Anatomical variations (narrow tunnel, persistent median artery), nerve compression susceptibility (diabetes mellitus, systemic neuropathy), systemic and endocrine diseases (pregnancy, amyloidal, hypothyroidism) or space-occupying lesions in the tunnel are some of the predisposing factors [5].

No gross anatomical abnormality is observed in the median nerve in the early phases of CTS, but within the process, demyelization and fibro sclerosis develop. In the chronic period permanent, sensory and motor function losses occur. Atrophy is typically located in the thenar muscles (''ape hand'' deformity). Although not innerved by the median nerve, atrophy also occurs in IOM muscles innerved by the ulnar nerve [13, 14].

In the literature, it is stated that atrophy and structural changes of hand muscles can be detected successfully by US [10, 15]. However, we cannot find a comprehensive study about the possible relationships between sonographic IOM/IMS measurements and hand grip strength. Seeing this gap in the literature; we primarily intend to detect possible relationships between hand grip strength and IOM/IMS measurements.

In this study, an examination was made of the alterations in the dimensions of the intrinsic muscles of hand that are not innervated by the median nerve before a visible thenar atrophy emerged. It was also aimed to determine the association between changes in dimension and loss of hand grip strength. In a review of literature review, no study was found which examined IOM dimensions sonographically and related them with loss of muscle strength. In the control group, there was a statistically significant relationship between IOM dimensions and muscle strength; as IOM dimensions increased, hand grip strength also increased. In the CTS patients, the IOM dimensions were significantly reduced but there was no significant relationship between the decrease in muscle strength and IOM dimensions. This is an unexpected finding. The small sample size of CTS patients can cause this result, but it is also possible that the decrease in hand grip strength becomes detectable after the muscle atrophy comes to some certain degree. Further prospective studies are needed to ensure this hypothesis.

In the literature review, no study was found which evaluated IMS sonographically, and investigated the normal dimensions of IMS and the relationship between these dimensions and grip. The current study can be considered to contribute to literature in these respects.

In the control group, a significant relationship was observed between IMS dimensions and grip strength and in CTS patients, the IMS dimensions were found to be significantly reduced compared to the control group. However, no significant relationship was determined between muscle strength decrease and IMS dimensions in the CTS patients. The small sample size of CTS patients might be the explanation for this result, but we think that it is also possible that the decrease in hand grip strength becomes detectable after the muscle atrophy comes to some certain degree. Further prospective studies are needed to ensure this hypothesis.

Detecting a significant difference between CTS and control groups in sonographically detected IMS and IOM values revealed that these parameters can/should be used for detecting the atrophy and loss of hand grip strength in CTS patients. Even though the muscle strength decrease in the CTS patients was not directly associated with the IOM and IMS dimension decrease in this study, we strongly believe that, this could be attributed to the small sample size. Likewise, the millimetric measurement values and closeness of quantitative measurements may also have resulted in an inability to detect an existing statistically significant relationship. And also, we think that further prospective studies following the change in IOM/IMS measurements with repetitive examinations can show the relationship in some stage of CTS.

The Limitations of the Study

This study has some limitations. The limited number of patients obscured statistical evaluation and relational determination in the CTS group. As all measurements were conducted by the same radiologist, inter-rater variability was not applicable. The results may have differed if conducted by a less experienced researcher, as the radiologist who took a leading role in the present study had 25 years of experience in the field. As the study sample was homogenized for age and gender, a very limited population data was analyzed.

Conclusions

In conclusion, IOM and IMS values are found to be related with hand grip strength and this relationship can be easily detected using proper sonographic methods. This can definitely help clinicians to plan or

direct treatment. Further studies investigating IOM and IMS on different pathologies affecting hand grip strength and hand muscles and investigations on larger samples will enrich the information about these parameters and would provide more evidence to support the current results.

Authorship declaration

All authors listed meet the authorship criteria according to the latest guidelines of the International Committee of Medical Journal Editors, and all authors are in agreement with the manuscript.

Conflict of interest

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Is group diabetes education effective on hemoglobin A1c level?

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ABSTRACT

Objectives. Diabetes education decreases hemoglobin A1c (HbA1c) level by 1% in patients with diabetes mellitus. In addition, education delays development or progression of complications by improving psychosocial, clinical, and behavioural aspects of diabetes mellitus, improves quality of life, modifies life style behaviours including healthy eating and regular exercise. In this study, we aimed to evaluate efficacy of diabetes group education programme called diabetes school on glycemic control by comparing HbA1c levels of patients with diabetes mellitus measured before and after education. ***Methods***. Electronic medical records of patients with DM who were registered to diabetes school executed by endocrine units of two hospitals between 2015 and 2017 were retrospectively evaluated. Diabetes school programme was composed of 90 minutes sessions a week for 4 consecutive weeks. Education sessions were executed in a didactic and interactive pattern. ***Results***. The attendees (n = 65) had signicantly lower HbA1c levels after the education programme (before 9.09 ± 2.46%, after 7.88 ± 1.90%; $p = 0.001$) than the non-attendees (n = 41) (before 8.96 ± 2.35%, after 8.35 ± 2.00%; $p = 0.091$). Insulin users had significantly higher baseline HbA1c values and benefited more than non-insulin users ($p < 0.0001$). ***Conclusions***: The diabetes school education programme has positive impact on glycemic control in patients with diabetes mellitus. A large team may lessen the burden of education sessions on health specialists. The school executed by a team consisting of specialists may reach a larger number of patients while the patients get the opportunity to repeat the sessions anytime they need.

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Key Words: diabetes education, hemoglobin A1c, diabetes school, group education

Introduction

Diabetes mellitus (DM) is a chronic disease which may be associated with serious comorbidities and the prevalence is progressively increasing worldwide [1]. In Turkey, the prevalence of DM increased dramatically from 7.2% to 13.7% according to the Turkish diabetes epidemiology (TURDEP) studies in 1998 and 2010 [2, 3]. Diabetes treatment is governed by glycosylated hemoglobin A1c (HbA1c) level, as the most important indicator of glycemic control. Target level is determined by age, associated comorbidities, and life expectancy [4]. Despite novel oral and injectable agents, increased awareness of

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insulinisation, and diabetes education, 50-70% of the patients still do not achieve target levels worldwide as well as in Turkey [3, 5]. Annual cost of DM, related comorbidities, and complications reached 10 billion Turkish liras according to the official insurance agency, Sosyal Güvenlik Kurumu [6].

Education influence health outcomes and the use of health services in patients with DM. Everyday the patients have to make decisions on nutrition, physical activity, and medications [7]. Furthermore, they have to manage DM related comorbidities such as hypertension and dyslipidemia and complications and make necessary arrangements [1]. There are insufficient data favouring either individual or group education regarding outcomes of DM [7]. The main issue is to find out the most effective method of education, that behavioural change, self management, and psychosocial outcomes benefit most [7].

The patients should receive diabetes education at the time of initial diagnosis, according to personal needs, and as diabetes therapy becomes more complicated [1]. In Turkey about 500 certified nurses provide diabetes education (Turkish Diabetes Nurse Association data). Growing population, increased DM prevalence, heavy outpatient burden, and short duration of outpatient visits lead to insufficient education. Transfer of intense information during short visits cause difficulties in comprehension and memorization. Health facilities provide different methods of education including individual and group education and diabetes school, a type of structured group education steered by Health Ministry.

In order to standardize diabetes education and guide health professionals in charge, Turkish Public Health Agency published Guide for Educators of Patients with Diabetes in colloboration with experts, organizations, and associations [8]. Education method and content advised in the guide is based on International Diabetes Education Standards published by International Diabetes Federation (IDF) [9].

In this study, we aimed to evaluate the effect of diabetes school education on glycemic control by comparing HbA1c levels measured before and within 6 months after completion of education.

Methods

Electronic medical records of 236 subjects, who attended diabetes school education programme executed by endocrinology units of Eskişehir Yunus Emre and Eskişehir State Hospitals between 2015 and 2017, were evaluated retrospectively. Although the main target population of education was patients with a diagnosis of DM, any other people including those with prediabetes and care-givers and relatives of patients with DM were also allowed for participation. Therefore only subjects over age 18 with a diagnosis of either type 1 or type DM for at least one year were selected. The school programme consisted of weekly executed 90 minute sessions for 4 consecutive weeks. The participants who attended at least 3 sessions were given certificates. One hundred six patients, who had HbA1c measurement within 3 months before and after the programme, were included to the study. They were categorized into 2 groups as attendees (n = 65) who completed the programme and as non-attendees (n = 41) who failed to do so.

The first session began with information given by an endocrinologist about definition of DM, subtypes of DM, signs and symptoms, and pathophysiological mechanisms. A certified dietitian informed about nutrition in DM. In the second session an endocrinologist described antidiabetic drugs and management of hypoglycemia. The session continued with information given by a neurologist regarding neurological complications. Third session began with information given by a specialist in sport medicine about the importance of regular exercise and exercise types. Information about insulin therapy, injection technique, and foot care was given by certified diabetes nurses. In the last session, a nephrologist described the role of kidney in diabetes, effect of diabetes on kidney function, and diabetic kidney disease. An ophthalmologist gave information about eye diseases frequently encountered in DM with special attention to retinopathy, prevention, and management of these disorders. The school programme completed after information regarding self monitoring of blood glucose and tips for life with diabetes was given by diabetes nurses. In all sessions, information was transferred in a didactic fashion along with visual supportive materials. The attendants were allowed to express themselves freely and ask questions during and after sessions.

HbA1c levels measured by HPLC within 3 months before and 6 months after diabetes school were compared along with age, gender, diabetes duration, treatment modality, and diabetic complications in patients with DM who completed at least 3 sessions of education.

Statistical Analysis

Table 1. The sociodemographic and clinical features and laboratory data according to attendance to the school

	Attendees (n = 65)	Non-attendees (n = 41)	*p*
Gender (F/M)	37/28	27/14	0.418
DM type (1/2)	4/61	NA	
Age	56.56 ± 10.63 (25-80)	56.17 ± 13.57 (21-76)	0.878
DM duration (years)	11.7 (1-36)	NA	
Treatment (n)			
OAD	25		
OAD+insulin	31	NA	
OAD+exenatide	1		
Insulin only	8		
Hypertension	29	NA	
HbA1c (%), before education	9.09 ± 2.46	8.96 ± 2.35	0.795
HbA1c (%), after education	7.88 ± 1.90	8.35 ± 2.00	0.228

Data are shown mean ± standard deviation (or range) or number. F = female, M = male, DM = diabetes mellitus, NA not available, OAD = oral antidiabetic drug, HbA1c = hemoglobin A1c

Normally distributed data (HbA1c and age) are shown as mean ± SD. Non-normally distributed data (duration of DM) is expressed as mean. Student t test was used for HbA1c and age in group analysis. For comparison of HbA1c measurements before and after the school programme, Wilcoxon signed ranks test was used for group analysis. General linear model for repeated measures was used for subgroup analysis (gender, insulin use). A p value less than 0.05 was assumed as statistically significant.

Results

The electonic database of 65 patients out 236 subjects, who completed at least 3 sessions after registration, was evaluated. The mean number of subjects who attended each session was 33. The sociodemographic and clinical features and laboratory data are shown in Table 1.

Data regarding retinopathy was present in 44%, diabetic kidney disease in 41%, and neuropathy in 40% of the attendees. Therefore the rates of retinopathy (n = 11, 16%), diabetic kidney disease (n = 8, %12), and neuropathy (n = 12, %18) low.

When HbA1c levels before and after the education programme were compared, the attendees had signicantly lower values (p = 0.001) than the non-attendees (p = 0.091). The attendees who had baseline HbA1c level over 8% (n = 38) showed greater reduction (before 10.75 ± 1.79%, after 8.71 ± 2.04%) than those with lower values (n = 27; before 6.75 ± 0.77, after 6.70 ± 0.71%) (p < 0.0001) although they had similar age and duration of DM.

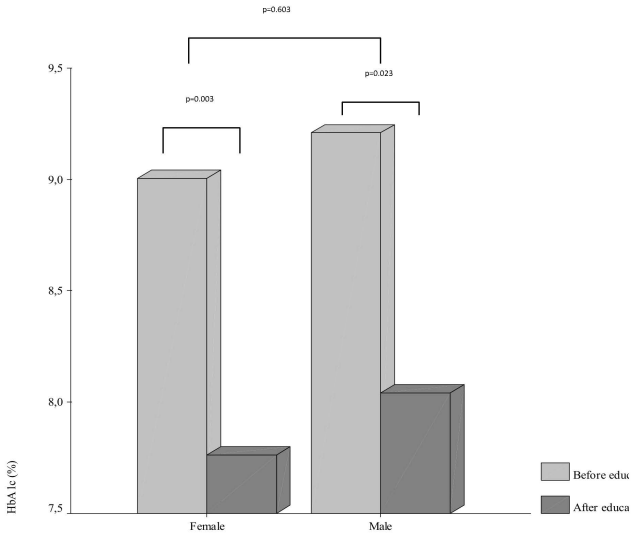

Figure 1. HbA1c levels before and after education according to gender

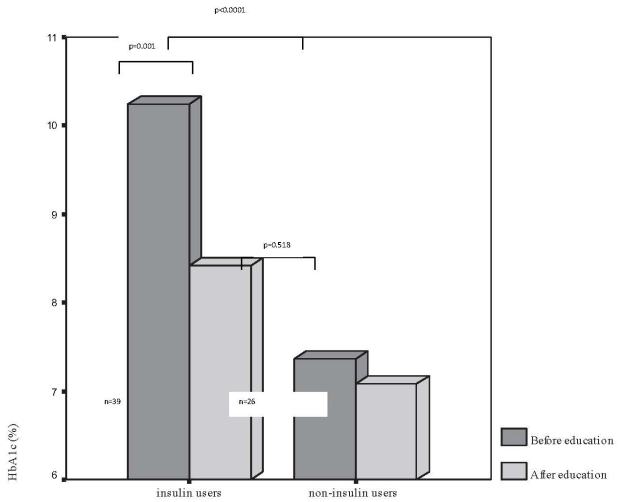

Figure 2. HbA1c levels before and after education according to insulin use

Both gender had significantly lower HbA1c values after completion of education, although female patients benefited nonsignificantly more than male counterparts (Figure 1). Insulin users had significantly higher baseline HbA1c values and benefited more than non-insulin users (Figure 2). Gender distribution and age were similar in both groups.

Discussion

Diabetes education is an indispensable component of management of DM as emphasized in various guidelines [9, 10-12]. Diabetes education can decrease HbA1c level by 1% in patients with type 2 DM [10]. In the literature decrease in HbA1c varies between 0.6 to 2.5% [7, 13, 14]. Beyond absolute values, statistical analysis showed variable results, for example while in one study 0.6% decrease in HbA1c was statistically significant, in another study 1.49% decrease in HbA1c was nonsignificant [15, 16]. One possible explanation might be the heterogenity of the studies regarding education content, duration of education and diabetes, modality of treatment, and HbA1c value before education. HbA1c close to the target level before education and progressive nature of the disease further complicates the evaluation of efficacy [17]. In this study we showed a statistically significant decrement of 1.21% in HbA1c which supports positive impact of diabetes school as a group education model on short term glycemic control.

Studies comparing the effect of group versus individual education on glycemic control yielded various results, some showed superior and some showed similar efficacy [11, 12, 15-18]. A meta-analysis showed significant decrease in HbA1c at 4-6 month and 1 year after education (mean: 1.4% and 0.8%, respectively) [13]. If education continued on annual basis, benefit on glycemic control sustained at 2 years of education (HbA1c 1% lower than baseline value) [13]. Significantly lower HbA1c was observed even at the end of 5th year in Trento group education model [20]. In another meta-analysis based on Cochrane database, HbA1c was reduced by 0.1% after individual education and 0.03% after group education over a span of 12-18 months [7]. Subgroup analysis yielded significant decrease in patients with baseline HbA1c higher than 8%. We also found that the patients with HbA1c value over 8% benefited diabetes school programme significantly more than those with 8% ≥. This finding may be due to higher motivation of patients to find a solution to uncontolled DM. However it is well known that efficacy of antidiabetic therapy is greater with higher HbA1c. Also patients with poor glycemic control frequently use insulin therapy and insulin is the most efficient mode of therapy in terms if HbA1c decrease. Therefore medical therapy not only before education programme but also after the programme should be taken into consideration in order to reach a definite conclusion about the role of education in HbA1c levels above 8%.

There are a few studies dealing with diabetes education in Turkey. In a study of 291 patients, HbA1c within 3 months before and after individual or group education was compared. HbA1c level did not decrease significantly (before 8.91 ± 2.34%, after 9.00 ± 4.44%) [21]. This study was executed in 5 centers from one city. The number of educators was 161 and most of them were not certified educators. When the educators were interrogated about the content of their education, it was found that only 29-70% of main topics of necessary information was given. Questionable sufficiency of the educators, non standardized education, and absence of HbA1c sampling time after education preclude us to reach a clear conclusion. Another study involving 25 patients, 40 minute sessions of individual education was conducted for 3 consecutive weeks. HbA1c decreased by 2.0% 8 weeks after completion of programme [22]. In another study consisting of two groups consisting 25 patients each, the attendees received weekly education sessions from one expert educator for 10 consecutive weeks. At 6 month following programme, HbA1c decreased by 1.2% while 0.4% decrease was observed in control group [23]. Our study share similar features with the two latter studies. We suggest that consistency in the structure and content of education programme may contribute to the success. We believe that standardization of diabetes school education programme nationwide along with improved techniques are the determinant of success.

In another study, education was given to 53 patients on insulin therapy individually at initial and in group at 1st and 3rd months [24]. Each group consisted 5 person and interactive modality was applied. At the end of 6th month, 16% decrease in HbA1c was observed in the intervention group and 2% increase was detected in the control group who did not complete education programme. In our study we obtained similar results and insulin users benefited education programme more than non insulin users (-1.82%, 14.7% decrease vs -0.29%, 1.83% decrease). These results suggest repetitive education and office visits contribute to the success of insulin therapy as an

effective treatment modality.

The main aim of diabetes education either in individual or group pattern is to achieve behavioural outcome after learning process [10, 15]. It is hard to accomplish and maintain behavioural change and the patients frequently cannot retrieve information learned earlier [11, 18, 25]. In our study we retrospectively evaluated only short term (6 months duration after education) effect of education on glycemic control. Since we did not take surveys of diabetes attitude, diabetes care profile, empowerment, and knowledge about DM, we cannot comment on psychosocial, clinical, and behavioural outcomes of diabetes school.

The advantages of group diabetes education are avoiding the overwhelming effect of continuously repetitive nature of individual education on health professionals and providing education for more people at one time [25]. Interactivitycontributes to positive dynamics [25].

A number of education models, which have similar content but vary in learning technique, duration, and frequency, have been developed. Active contribution of patients and patient-centered approach should be favoured rather than didactic teaching model [9]. Therefore we combined both didactic teaching method and interactive approach by question and answer method.

Education delays development and progression of complications, improves quality of life, modifies life style behaviours including healthy eating and regular exercise, decreases diabetes associated stress and depression, enhances self- and empowerment skills, management and aids in healthy coping with problems by influencing psychosocial, clinical, and behavioural aspects of DM in positive manner [26]. Education is a cost-effective way of reducing hospitalizations and complications [26]. The short term nature of our study preclude us to make a comment on hospitalization and complication rates.

The Limitations of the Study

There are some obstacles in group education. Non homogenous composition in terms of sociodemographic features (age, education, numeracy and medical literacy, language skills, cultural behaviours) and attitude (unwillingness to contribute, interrupting people's speaking, struggle to participate etc.) may preclude a patient to share his/her own experience with others. [11, 27]. We did not assign the patients according to their sociodemographic features before admission. Therefore our groups are heterogenous. Data regarding education, numeracy, and medical literacy were unavailable.

Conclusions

The positive impact of diabetes school education programme executed by Health Ministry and Public Health Agency on glycemic control is compatible with the results of individual and group education programmes with different concepts and design. In other studies, education team consisted of at least 1 up to 3 health professional including dietitian, diabetes nurse, and physician. Our team consisted of 6 physician specialists, 1 dietitian, and 2 certified nurses. A large team may lessen the burden of education sessions on health specialists.

However mid-term and long-term studies are needed to evaluate the effects of diabetes school programme on the targets of regarding quality of health, frequency and severity of complications, weight, dyslipidemia, and blood pressure control, cessation of smoking, and knowledge of diabetes.

We suggest that the school model executed by a team consisting of specialists may reach a larger number of patients while the patients get the opportunity to repeat the sessions anytime they need.

Authorship declaration

All authors listed meet the authorship criteria according to the latest guidelines of the International Committee of Medical Journal Editors, and all authors are in agreement with the manuscript.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Dental students' perceptions on preclinical restorative dentistry course: Biruni University case

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ABSTRACT

Objectives. The student's perspectives of their restorative dentistry education would be an important source of information for evaluation of preclinical curriculum. Thus, the aim of the present research was to obtain information from second-year students at Biruni University dental school about their preclinical restorative dentistry program perceptions, levels of stress during preclinical courses and preparedness for upcoming restorative dentistry courses in clinics. ***Methods.*** The present survey was carried out on the second year students in dental school in Istanbul. The survey composed of items regarding students' perspectives regarding to the levels of their stress in preclinical restorative dentistry courses as well as preparedness for future restorative dentistry courses in clinic. Student's t-test was applied to the data. ***Results.*** Students found posterior composite restorations lessons more stress-full than amalgam restoration lessons. They expressed that knowledge they obtained from the lectures is adequate for preclinical courses and they felt themselves prepared for the restoration of posterior teeth in clinic. ***Conclusions.*** Second-year student's perceptions of preclinical restorative dentistry curriculum in Biruni University were highly positive. The student's perspectives of their restorative dentistry curriculum would be an important source of information for dental faculty staff in order to establish an adequate preclinical curriculum for the students who start delivering public patient care in the future.

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Keywords: Restorative dentistry, preclinical course, student perception

Introduction

Preclinical courses are the essential components of restorative dentistry education in dental schools. Preclinical courses enable students to acquire and develop their fundamental dental skills, gain knowledge about the clinical aspects of to restoring carious and/or defective teeth [1, 2]. These fundamental skills are taught through lectures, and simulated exercises in a preclinical courses using either artificial or extracted natural teeth, prior to the student delivering care to an actual patient in the clinic. Thus, for the dental student who will deliver care to patients in clinics, it is desirable that preclinical education prepare students individually ready for beginning to patient care [3].

Preclinical restorative dentistry courses present in the second-year and third-year curriculum programs

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of dentistry school in dental school of Biruni University that was settled in 2014 in Istanbul, Turkey. The aim of preclinical restorative dentistry courses in the second year curriculum concentrates to provide knowledge and skills in the restoration of posterior teeth with using amalgam material or resin composites, while courses in third year are decided to provide knowledge and skills of restoration of anterior teeth and simulation of clinical restoration procedures with using a mannequin model. During the second and third year, theoretical restorative dentistry lessons which are prepared by reviewing classical textbooks are given weekly. These lessons are related to subsequent preclinical sessions as well as other topics of restorative dentistry. However, at the start of each preclinical course session in which a restorative procedure will be presented firstly, demonstration and PowerPoint presentations are performed via a video camera in preclinical session according to course curriculum (Table 1). Students should complete restorative procedures for different restoratives in plastic or natural teeth. Two groups of each 40-45 students are supervised by two fixed instructors over 32-week course in second year at the dental school of Biruni University. At the end of each session, each student performance is reviewed by the same instructor and provided feedback for each tooth in the session for the first 16-week period of the restorative dentistry course. In the second 16-week period of restorative dentistry course, seasonal performances of students were not reviewed on weekly, however, an additional practical exam is utilized to review overall performances of students through the second midterm. The evaluation of weekly performances of students was done using assessment point sheets for each restorative procedures in the preclinical restorative curriculum by one instructor through the academic year.

Dental student perspectives on the structure and content of their dental education experience are an important part of an evaluation of the curriculum [1]. Despite that, it is stated that student perspective on

Table 1. Preclinical restorative dentistry curriculum for second year student at Biruni University (2016-2017)

Week	Laboratory topic	Activities
1	Introduction to restorative dentistry course.	
2 - 4	Occlusal cavity and class V cavity preparation on plastic teeth (for amalgam)	Tooth 35, 35, 36, 37, 46, 37 O
5 - 7	Proximal cavity preparation on plastic teeth (for amalgam)	Tooth 24 , 25 MO, 26, 27 DO, 34, 35, 36 MO, 37 DO, 44, 45, 46, 47 MO
8	Reparation week. Students with unacceptable performance in the previous lessons redo their preparations in this week.	
9	Midterm practical exam	Tooth 45 DO cavity preparation, 46 MOD and 47 DO cavity preparations with base placement
10 -12	Complex cavity preparation on plastic teeth (for amalgam)	Tooth 14, 15 DO, 16 DOP+MO, 17 DO, 45 MOD, 46 O, 47 MOD, 21, 22, 23 ML, 26 MOD
13-16	Cavity preparation and placing of base material on plastic teeth (for amalgam)	Tooth 34 MO, 35, 36, 37, 14 , 15 O, 16 MOD, 17 O, 24 MO, 25 O, 26 MOD, 27 O
17-20	Cavity preparation, placing of base material and amalgam restoration on plastic teeth	Tooth 44 O, 45 DO, 46 DO, 47 O
21	Amalgam polishing and sectioning of tooth in sagittal on natural teeth	Polishing amalgam restorations performed in the previous session.
22-23	Caries removal on natural teeth	Eight molar, eight premolars
24-25	Composite restoration on natural teeth	Eight molars, eight premolars
26-27	Occlusal composite restoration on plastic teeth	Tooth 14, 15, 16 , 24, 25, 26 O
28-31	Proximal composite restoration on plastic teeth	Tooth 35, 36, 37 MO, 45 DO, 46 MOD, 47 MOD, 14 DO, 15 MO, 16 MOD, 17 MO
32	Additional practical exam (composite restoration)	Tooth 15 DO, 16 MOD composite restorations
33	Final Exam	Tooth 15 DO cavity preparation with base placement, 16 DO composite restoration, 17 DO amalgam restoration

D = distal, L= lingual, M =mesial, O = occlusal

their educations generally undocumented in the literature. Because some sources suggested that dental students are not satisfied with their education [4], while others stated that students provided positive feedback about their experiences in dental schools in the form of anecdotal reports [1]. Therefore, negative perceptions that might have unexpected results on performances of students throughout their dental educations and their total satisfaction with dentistry may stay invisible. Thus, the aim of the present study was to gain knowledge about students' perception on preclinical restorative dentistry courses in dental school of Biruni University.

Methods

The present research was carried out on the second year students at the dental faculty of a foundation university (Biruni University, Faculty of Dentistry). A survey of Dikbas *et al.* [5] was modified to assess students' perceptions of the restorative dentistry curriculum. Nameless survey forms were divvied to 84 students of the dental school at the last week of the academic year.

The survey continued over the length of preclinical course. Students were instructed that completing and returning survey were not mandatory and the process had no association with grading before completing the survey forms. It was expressed to the students at the start of the survey that the privacy of the participating students was guaranteed and all data would be retained rigorously private.

The survey composed of 9 items regarding their thoughts about the adequacy of knowledge they received from their preclinical training and their stress levels in preclinical courses. Items were commonly focused on students' perceptions of their preparedness in terms of hand-skills and clinical practices. The first 8 items were multiple-choice with 3 answer options rated from 1 to 3 and students were asked to make scorings in amalgam and composite restorations, individually. The 9th question was open ended and inquired about students' personal opinion and

Table 2. Evaluation of the answers on amalgam and posterior composite restorations

Questionnaire items		Students (%) (n=79)		
		Amalgam restoration	Posterior composite restoration	*p* value
Please rate your level of stress during the preclinical course?	Not stressful	46.8	34.2	**0.033**
	Stressful	43.0	44.3	
	Very stressful	10.1	21.5	
What do you think about the length of the preclinical courses?	Too short	25.3	38.0	**0.006**
	Just right	73.4	62.0	
	Too long	1.3		
Do you think you have enough interaction about your preclinical work with your instructors during preclinical courses?	Not enough	7.6	5.1	0.319
	Just right	74.7	72.2	
	More than enough	17.7	22.8	
Do you feel the knowledge you have obtained from the lectures is adequate for preclinical courses?	Not adequate	2.5	-	0.951
	Just right	69.6	71.8	
	More than adequate	26.6	28.2	
Do you think the knowledge you gained from the lectures is helpful in preparing for clinical practice?	Yes	87.3	87.3	1.000
	No	3.8	3.8	
	Not certain	8.9	8.9	
How prepared (from your pre-clinical experiences) do you feel about treating patients in the clinic? (self-confidence)	Unprepared	30.4	32.9	1.000
	Just right	49.4	44.3	
	Well prepared	20.3	22.8	
Do you think you have enough clinical-skill (hand-skill) training to treat patients in the clinic?	Not enough	19.0	24.1	0.585
	Just right	68.4	63.3	
	More than enough	12.7	12.7	
How helpful are demonstrations in helping you understand pre-clinical and clinical knowledge and skills?	Not helpful	8.9	7.6	0.879
	Helpful	69.6	73.4	
	Very helpful	21.5	19.0	

Students t-test was used ($p < 0.05$).

suggestions for the improvement of the preclinical restorative dentistry courses.

Statistical Analysis

The percentages were obtained with respect to each question. Data were analyzed using SPSS version 16. Differences between group means were analyzed using students t-test. The significance was set at $p<0.05$.

Results

The response rate of this questionnaire was 94%. Findings of student's answers to the questions were summarized in Table 2. Regarding to stress levels during preclinical laboratory exercises, students reported significantly higher stress levels for posterior composite restorations lessons compared amalgam restoration lessons ($p = 0.033$). Thirty-eight percent of students expressed that length of preclinical courses of composite restorations were short with significantly different when compared to amalgam restoration courses (25.3%) ($p = 0.06$). Only 5.1% and 7.6% of the students stated that they have not enough interaction work their preclinical performance work with their instructors during laboratory exercises for posterior composite and amalgam restorations, respectively. Almost all of the students expressed that they felt that the knowledge they had gained from lectures were adequate for laboratory exercises for both amalgam and posterior composite lessons. The majority of students thought that the knowledge they obtained from the lectures was helpful in preparing for clinical practice for both amalgam (87.3%) and posterior composite restorations (87.3%). Almost two out of three of the students reported that they felt "just right" or "well prepared" about treating patients in the clinic for amalgam and composite restoration respectively. With similar ratings, students stated that they gained enough clinical-skill (hand-skill) training to treat patients in the clinic for both materials. The majority of students expressed that they found demonstrations in helping them understand pre-clinical and clinical knowledge and skills.

Discussion

Numbers of newly settled dentistry faculties in state zone or in the private zone in Turkey have increased during the last decade. Majority faculty staff of these new dental schools would be considered as a new generation academics with little or no teaching experience. Thus, a training of a new generation of dental faculty staff appeared an urgent question to be solved. However, training and teaching experiences in these newly settled dental schools at different departments in terms of students' perspectives would be an important information for assessing quality of dental education curriculums in these dental schools.Therefore, in this study, information about second year-students perspectives of their restorative dentistry preclinical course and stress level during these courses and preparedness for future clinical patient care in restorative dentistry was obtained in Biruni University which was settled in 2014.

Preclinical courses of restorative dentistry are interactive lessons in their nature as students often ask questions about their performances to the instructors during the course. Instructions should check whether each student gains learning objects in preclinical curriculum and able to apply them on their weekly performance correctly to this interaction. If a student realize that he/she achieved to learn and apply preclinical lesson objectives on his/her weekly performance by the interaction with the instructors during course, it's likely that student feel and see that theoretical knowledge which they obtained from lectures are adequate for preclinical courses and they feel self-confidence for delivering patient care with restorative dentistry procedures they experienced in preclinical courses. Thus, the interaction of students with their instructors during preclinical courses seems to be a pivotal educational process to prepare students for clinical service care. The majority of the students enrolled to this survey reported that they had an enough or more than enough interactions with their instructors. The high positive reports also exist for regarding the helpfulness of lectures in preparing them for clinical practice. A previous research stated that students' rating for this interaction could be lower in State universities.They suggested that a high number of students and low number of instructors in the State schools would be reasons for lower interaction ratings by students. However, in Biruni University case presented in this study, there were only two instructors and eight-five second year students in restorative dentistry preclinical course. Thus, it can be suggested that despite low number of instructors and high number of students, high student's rating for

interaction during courses could be achieved in some cases.

Dental students should acquire of psychomotor skills during the preclinical course of restorative dentistry to be prepared to deliver patient care in the clinics [6, 7]. According to the Suksudaj *et al.* [6], several important factors can influence skill acquisition of students, including student-related factors, i.e. level of innate ability and motivation, and non-student related factors, i.e. learning environment. According to learning theories, students should have cognitive ability to understand procedures regarding a particular task [8]. Therefore, performing demonstrations of restorative dentistry procedures; i.e. incremental placing of resin composite into the prepared proximal cavity at the preclinical courses would increase students' cognitive abilities, helping in improvement their psychomotor skill and increasing feeling preparedness of the students for near future clinic practice. In the present study, most of students found demonstrations "helpful" or "very helpful" in helping them understand preclinical and clinical knowledge and skills for amalgam and posterior composite restorations.

Another factor that would have a significant effect on acquisition of skill in restorative dentistry is a motivation [9]. Motivation means the effort which is separated to tasks. High effort or motivated people tend to reach a high level of performance [6]. In this survey, almost one of each three students reported that the length of the preclinical course is short, although three hours were allocated to preclinical course every week. This demand of students for a long preclinical course may indicate that motivation of students is high. This would contribute high positive perspectives and high rate of felling preparedness for the clinic practice of students for restorative dentistry courses in Biruni University.

For an instructor interest, having information about how prepared his students felt about delivering patient care in the clinic is an important merit him assessing his education program. This study revealed that two thirds of students reported that they did feel prepared or well prepared to perform amalgam and posterior composite restoration in the clinic. Similar ratings were reported when they asked if they think have enough hand-skill training to treat patients in the clinic. There is an obvious link between feeling preparedness and having enough hand-skill in the perspectives of the students in restorative dentistry. However, some other factors which are related to the medical condition of students would have an important influence on skill acquisition and feeling preparedness for clinical practices. These are included eye defects, i.e. myopia and astigmatism, and unexplained hand tremor. Even though a student has a enough cognitive ability, motivation, and perceptual speed ability is required to find the most effective way to achieve the task, these medical conditions would reduce psychomotor ability of a student [6], thus preventing student to assess their work accurately or prevent perform high quality work.Therefore, the author suggests that instructors should determine these students at the earliest preclinical course session and inform their parents about this issue to improve skill acquisition of these students.

Conclusions

The present survey would be the first research regarding to students' perceptions of preclinical restorative dentistry courses among Turkish Dental Schools. Obtaining information dental students' perceptions of feeling being preparedness and their level of stress during their preclinical courses prior to delivering patient care in the clinic would lead to preclinical restorative dentistry curriculum. Based on the findings, second-year student's perceptions on preclinical restorative dentistry curriculum in Biruni University were highly positive. The author suggests that similar questionnaires would be carried out in other newly settled Turkish dental schools.

Conflict of interest

The author disclosed no conflict of interest during the preparation or publication of this manuscript.

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Correlation between metabolic syndrome disorder and circadian rhythm of physically disabled individuals

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ABSTRACT

Objectives. The aim of this study was to examine the correlation between sleep disorder and metabolic syndrome disorder in physically disabled people. ***Methods.*** The study was conducted among physically disabled persons who were selected from the Education and Rehabilitation Centre of Disabled People in Çorum, a city located in the central north of Turkey. Sleep quality is assessed with Turkish version of Pittsburgh Sleep Quality Index. The metabolic syndrome disorder, weight circumference and blood values of participants are examined by three health personnel from a private hospital in Çorum. ***Results.*** One hundred and three persons (56 M, 47 F) participated in this study. Metabolic syndrome disorder was found in 23 (22.3%) participants. Forty (38.8%) participants had bad sleep quality. The correlation between circadian rhythm and metabolic syndrome disorder was significantly positive ($p<0.01$). It was found that the persons who have a bad sleep quality spend more energy than the persons who have good sleep quality ($p=0.001$). Energy expenditure of the participants with metabolic syndrome disorder is higher than without metabolic syndrome disorder ($p<0.001$) at the time of sleeping. ***Conclusions.*** This study confirms the positive relationship between circadian rhythm irregularity and metabolic syndrome disorder. Also, the study supports the idea that circadian rhythm irregularities cause an increase in daily energy expenditure which leads further metabolic syndrome disorder.

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Keywords: Circadian rhythm, metabolic syndrome disorder, energy expenditure, disabled people

Introduction

Circadian rhythm is one of the most important abilities in adaptation to environment and survival [1]. Under current conditions, circadian rhythm goes through an endogenous biological process of 24 hours. Its oscillation changes according to environmental factors such as light, temperature or food, so it provides a selective advantage in the evolutionary process [2-5]. Especially sleep cycle is the primary process regulated by circadian rhythm [6, 7] and sleep disturbance is accepted as an indicator of circadian rhythm irregularity.

Circadian rhythm has a regulatory impact on the many functions of the body such as body temperature, brain activity, hormone release, energy consumption, energy metabolism which is in relation to hormones, lipids, and cell reproduction [6, 7]. For this reason,

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circadian rhythm irregularity is thought to cause many functional disorders in the body. Many studies found that glycogen is affected by circadian rhythm irregularities [8-10]. It has also been showed that sleep disturbance contains within itself a high mortality risk due to obesity, hypertension, diabetes and cardiovascular diseases [11-15]. Following studies revealed a further effect of circadian rhythm on diverse metabolic systems. Because circadian rhythm regulates energy balance and metabolic system of peripheral tissues. It also helps maintenance of metabolic stability by regulating production and activity of metabolic enzymes (e.g. glycogen phosphorylase, lactate dehydrogenase, Acetyl-CoA carboxylase, cytochrome oxidase, malic enzyme, glucose-6-phosphate dehydrogenase) and transport systems of cells. These enzymes and transport systems join to the regulation of amino acids, drug and toxin metabolism, cholesterol metabolism, citric acid cycle, glycogen, and glucose metabolism [4].

Some studies focussed on diverse metabolic disorders, dealt with the correlation between metabolic systems and circadian rhythm. In these studies, one of the most analysed metabolic subjects is glucose metabolism. It is identified that daily 4-hour-sleep is related to decreased glucose clearance and glucose sensitivity [16-18]. In addition to this, findings show that circadian rhythm irregularities trigger the metabolic disorders such as obesity, type 2 diabetes, and cancer [17, 19, 20].

A metabolic syndrome disorder covers many symptoms of different metabolic disorders and is associated with increased risk of having at least one of those metabolic disorders. People with metabolic syndrome disorder (MetS), for example, catch the disease of type-2 diabetes 5 times easier and of cardiovascular 2 times easier [21]. Common symptoms of MetS are identified as abdominal obesity, glucose intolerance, dyslipidemia, coronary artery disorder, diabetes mellitus and hypertension [22]. Due to the rate of incidence of these symptoms in both MetS and circadian rhythm irregularities, a possible correlation between them is analysed in a study. Results reveal only a possible and bi-directional link [23]. Welsh *et al.* [24] states in his study that disruption of circadian rhythm causes a vicious cycle by leading to MetS which are further causing the maintenance of circadian rhythm irregularities. The aim of this study was to reveal the form of the above-explained relationship, especially in physically disabled people.

Methods

This study approved by the ethical committee of Okan University Institute of Health Sciences (research protocol number: 75, date: March 30, 2016). The study was conducted among physically disabled persons who were selected from the Education and Rehabilitation Centre of Disabled People in Çorum, a city located in the central north of Turkey. Data gathering process began in April 2016 and continued until June 2016. Totally 103 persons (56 M, 47 F) participated in the study. The age of participation varies between 18 to 74. The purpose and procedure of the study were explained in detail to all participants. In the study, participants' sleep patterns are treated as an indicator of circadian rhythm. The Turkish version of Pittsburgh Sleep Quality Index [25] is used to evaluate circadian rhythm of the participants. Each one of the participants and one of its immediate relatives answers the questions of the index. The index is formed to assess sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, sleeping medications and daytime dysfunction factors. Those who score 5 or less from the participants were rated as "good" and then those who score 5 points, or more were rated "bad". Bad sleep indicates a high sleep disturbance at least in the two factors or mild sleep disturbance in the factors more than three.

Metabolic syndrome disorder is identified according to criteria of Adult Treatment Panel III in National Cholesterol Education Program. According to these criteria, people are diagnosed with MetS who show three of five symptoms. The symptoms are sorted as following: a) higher blood pressure (BP) than 130/80 mmHg, b) higher triglyceride level than 150 mg/dl, c) higher blood glucose level than 110 mg/dl, d) lower HDL than 40 mg/dl for men and 50 mg/dl for women, e) higher waist circumference than 102 cm for men and 88 cm for women.

In this context, waist circumference of each participant is measured, and blood sample of each is taken. Eight-twelve hours fasting blood samples were taken as 8 ml with yellow-capped tubes by three health personnel from a private hospital in Çorum. Monitoring of blood pressure and measurement of waist circumference are also done by the same health personnel. Fasting blood glucose, triglyceride, HDL cholesterol and LDL-cholesterol levels are analysed with the Roche integra 800 machine. Blood pressure is measured by Erka D-83646 Bad Tölz.

In the study, participants' daily energy expenditure

is also analysed. For this purpose, the daily nutritional values of the participants are calculated during the study.

Statistical Analysis

The data is analysed through SPSS v.22 statistic programme. Descriptive statistics are presented with a number, percentage, mean and standard deviation values. They are used to evaluate the data. To understand whether data show normal distribution or not, Kolmogorov-Smirnov Z test is applied. In all analyses, 5% significance value is used to evaluate results.

Results

There was metabolic syndrome disorder in 23 (22.3%) participants (Tables 1 and 2). A significant difference between the systolic blood pressure, diastolic artery pressure, fasting blood glucose, HDL cholesterol and triglyceride values of participants with MetS and without MetS was found ($p < 0.01$)

Forty (38.8%) of the participants had bad sleep quality (Table 3). There was no significant difference between male and female participants in terms of sleep quality and MetS ($p > 0.05$). Based on these results, the relationship between sleep quality and MetS analysed with Pearson's Chi-Square Test. There was a significant correlation between sleep quality and MetS ($p < 0.01$). This ratio is also similar for both male and female participants ($p < 0.05$).

Participants' energy expenditure related to sleep quality and MetS are analysed (Table 4 and Table 5). Energy expenditure of participants who have bad sleep quality and good sleep quality is compared through independent sample t-test. The results show a significant difference between two groups in terms of daily energy expenditure ($p = 0.001$). Daily energy expenditure of participants who have bad sleep quality (mean: 2210 ± 569) is higher than participants who have good sleep quality (mean: 1370 ± 500). Daily energy expenditure of participants with MetS and without MetS was also compared. The results show that participants with MetS have higher daily energy expenditure than participants without MetS (mean: 2160 ± 703) vs. mean: 1562 ± 597; $p < 0.001$) (Table 5).

Discussion

Irregularity in sleep cycle was interpreted as an irregularity in circadian rhythm in this study. Because this interpretation comes from a significant correlation between circadian rhythm disturbance and metabolic syndrome disorder. This finding is also supported by some previous studies. In their study, Hung et al. [26]

Table 1. Distribution of metabolic syndrome criteria (n = 103)

Metabolic Syndrome Criteria	Data
Waist Circumference (cm)	89.86 ± 16.65 (60-129)
Systolic artery pressure (mmHg)	119.51 ± 17 68 (90-170)
Diastolic artery pressure (mmHg)	68.35 ± 12.61 (50-100)
Fasting Blood Glucose (mg/dl)	90.18 ± 25.33 (46-263)
Normal	93 (90.3%)
Low	10 (9.7%)
HDL (mg/dl)	22.1 ± 91.1
Normal	61 (59.2%)
>150	42 (40.8)
Triglyceride (mg/dl)	158.64 ± 105.90 (51.2-661.3)
Normal	64 (62.1%)
High	39 (37.9%)
Metabolic syndrome	
No	80 (77.7%)
Yes	23 (22.3%)

Data are shown mean ± standart deviation (min-max values) or number (percent).

Table 2. Metabolic syndrome criteria of individuals with metabolic syndrome disorder

Participant Number	Sex	Waist Circumference (cm)	Blood Pressure (mmHg)	Glucose (mg/dl)	HDL (mg/dl)	Triglyceride (mg/dl)
1	Female	95	140/80	115	48	115
2	Female	99	110/60	122	51	194
3	Female	100	110/60	108	48	376
4	Female	104	150/80	116	41	144
4	Female	116	110/70	95	35	215
6	Female	92	140/90	89	32	221
7	Female	89	130/60	114	64	176
8	Female	129	130/70	93	30	266
9	Female	102	130/60	93	41	177
10	Female	117	130/70	139	48	131
11	Male	114	120/70	73	30	482
12	Male	117	160/100	85	22	406
13	Male	115	120/80	99	35	211
14	Male	112	140/80	140	38	205
15	Male	117	130/80	97	34	335
16	Male	114	130/70	67	39	157
17	Male	118	140/90	84	37	165
18	Male	107	130/70	76	39	151
19	Male	115	150/80	95	51	245
20	Male	119	170/90	130	43	225
21	Male	120	150/90	93	34	241
22	Male	114	150/90	193	40	190
23	Male	120	160/90	68	36	161

reported a higher risk for people who have bad sleep quality. Jennings *et al.* [27] also stated that bad sleep quality increases the prevalence of MetS [27].

Because of the relationship between circadian rhythm and MetS, the body needs more energy due to lack of sleep. In other words, energy need is found to be related to sleep deprivation. Experimental studies on sleep restriction show a negative correlation between sleep deprivation and appetite-related ghrelin and leptin hormones and between total energy intake and body weight [28-30]. Furthermore, it is stated that this energy requirement is met by increased consumption of total fat, saturated fatty acid, and carbohydrate-rich foods [31]. Accordingly, many studies on circadian rhythm irregularities that cause sleep disorders present that these irregularities also

Table 3. Distribution of sleep quality criteria (n = 103)

	PSQI score			
Sleep Quality Criteria	**0**	**1**	**2**	**3**
PSQI - Sleep Quality	26 (25.2%)	66 (64.1%)	6 (5.8%)	5 (4.9%)
PSQI - Sleep Latency	43 (41.7%)	21 (20.4%)	33 (32.0%)	6 (5.8%)
PSQI - Sleep Duration	71 (68.9%)	13 (12.6%)	17 (16.5%)	2 (1.9%)
PSQI - Habitual Sleep Efficiency	70 (68.0%)	18 (17.5%)	7 (6.8%)	8 (7.8%)
PSQI - Sleep Disturbances	14 (13.6%)	83 (80.6%)	6 (5.8%)	0 (0%)
PSQI - Use of Sleeping Medications	49 (47.6%)	48 (46.6%)	1 (1.0%)	5 (4.9%)
PSQI- Daytime Dysfunction	44 (42.7%)	55 (53.4%)	3 (2.9%)	1 (1.0%)
PSQI total score				
Mean		5.15 ± 2.99		
Range		0-13		
Sleep Quality				
Good		63 (61.2%)		
Bad		40 (38.8%)		

Data are shown as mean ± standard deviation or number (percent). PSQI = Pittsburgh Sleep Quality Index

Table 4. Carbohydrate, protein and fat requirements for sleep quality (n = 103)

		Sleep Quality					
		Good			Bad		
		Min-Max	Median	Mean±SD	Min-Max	Median	Mean±SD
Male (n = 56)	Carbohydrate %	26-58	43.5	44.13 ± 6.39	37-59	50.5	48.94 ± 5.02
	Protein %	10-25	19	18.84 ± 3.13	15-21	18	17.56 ± 1.65
	Fat %	27-49	36.5	36.95 ± 5.10	25-43	34	33.72 ± 4.56
Female (n = 47)	Carbohydrate %	31-53	43	42.72 ± 6.85	32-55	49	46.64 ± 6.87
	Protein %	15-27	17	18.32 ± 3.34	14-23	18.5	18.18 ± 2.28
	Fat %	32-49	39	39.24 ± 4.98	28-47	34	35.59 ± 6.07
Total	Carbohydrate %	26-58	43	43.57 ± 6.56	32-59	50	47.68 ± 6.15
	Protein %	10-27	18	18.63 ± 3.20	14-23	18	17.90 ± 2.02
	Fat %	27-49	38	37.86 ± 5.14	25-47	34	34.75 ± 5.46

Table 5. Evaluation of daily energy expenditure according to sleep quality and MetS (n = 103)

			Energycal/day				
Feature		**n**	**Min-Max**	**Median**	**Mean±SD**	***t***	***p***
Sleep Quality	Good	63	483-2964	1329	1370 ± 500	-7,880	0.001
	Bad	40	563-2963	2264	2210 ± 569		
Metabolic Syndrome	No	80	482-2964	1499	1562 ± 597	-4,062	< 0.001
	Yes	23	1088-2961	2296	2160 ± 703		

t = Independent t-test. MetS = metabolic syndrome disorder, n = number of participant

have consequences for night eating syndrome [7, 32-34]. These interlinked disorders further increase the risk of metabolic disorders such as obesity and cardiovascular diseases. As a result, there is a causal correlation between increased energy requirement and sleep disturbance. Thus, daily energy consumption of participants is also researched in our study. The study proves that both bad sleep quality and MetS are causally correlated with energy consumption. The daily energy consumption of participants who have bad sleep quality and MetS is higher than the participants who have good sleep quality and no MetS. These findings support the previous assumption and indicate a chain of reaction due to irregularities of circadian rhythm.

Conclusions

The results of this study contribute to better understanding the relationship between circadian rhythm and metabolic syndrome disorder. Many parameters of this relationship need to be studied especially in terms of causal relation. Because, energy consumption is resulted from disturbance of metabolic balance and lead to circadian rhythm irregularities. A more comprehensive study seems necessary to understand the nature of this causal relationship.

Conflict of interest

The author disclosed no conflict of interest during the preparation or publication of this manuscript.

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Clinical presentation of tuberculosis: a nine-year single-center experience

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ABSTRACT

Objective. The aim of this study was to determine the clinical presentation of tuberculosis cases from our center for the last nine years. ***Methods***. This study was set as descriptive and retrospective. The data was obtained from the hospital records. Subjects who had been diagnosed as tuberculosis and received treatment in our center between the years 2007 and 2015 were included. The cases were classified as newly diagnosed, relapse, transferred, and returning after default. ***Results***. There were 276 (171 males and 105 females) patients with a mean age of 41.5 ± 19.2 years. Pulmonary involvement is the most common presentation and seen in 155 (56.2%) patients. Lymph node and pleura are the most common extrapulmonary involvements those are seen in 53 (19.2%) and 23 (8.3%) patients, respectively. Number of the cases seems to decreased after 2012. Most (85.1%) of the patients were newly diagnosed. Among the subjects, 55.2% of them had bacteriologic diagnosis, 35.1% had histopathologic diagnosis. Two subjects died during the treatment period whereas 274 of them completed the treatment program. ***Conclusions***. Our results show that tuberculosis is seen mainly in the adult age group. While pulmonary involvement is the most common presentation, lymph node and pleura involvements are the most common extrapulmonary presentations. Number of the tuberculosis seems to decrease for the recent years. Strict preventive measures and treatment strategies should be administered.

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Keywords: Tuberculosis, pulmonary involvement, Mycobacterium tuberculosis, extrathoracic tuberculosis, lymphadenitis, treatment strategy.

Introduction

Tuberculosis still remains a considerable health problem in spite of the strict preventive measures and treatment strategies [1]. Previous studies have already reported the clinical and demographical features, and management of tuberculosis in detail [2-5]. However, recent studies focused on the increased incidence of tuberculosis in the recent years [4-7]. Therefore, the aim of this study was to determine the clinical presentation of tuberculosis cases from our center for the last nine years.

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Methods

This study was designed as descriptive and retrospectively. The data were obtained from the hospital records. Subjects previously diagnosed with tuberculosis and received treatment in our center (Elbistan, Turkey) between the years 2007 and 2015 were included. Subjects with missing data regarding the diagnosis and clinical involvement, and transferred to other clinics for their treatments were excluded. Age, gender, year, tuberculosis involvement (thoracic, lymph node, pleura, bone, etc.), and diagnostic method (histopathological, microbiological) have been noted. The cases were classified as newly diagnosed, relapse, transferred, and returning after default. This study protocol was approved by the local ethics committee.

Statistical Analysis

SPSS version 16 (SPSS Inc., Chicago, IL, USA) was used for the statistical analyses. Data were expressed as mean ± standard deviation or percentage. Chi Square test was used to compare categorical variables between the groups. A p value of 0.05 was set as significance.

Results

A total of 276 (171 males and 105 females) patients with a mean age of 41.5 ± 19.2 years were included in this study. Clinical and demographical features are shown in Table 1. Pulmonary and extrapulmonary involvements are shown in Tables 2 and 3. Pulmonary involvement is the most common presentation, and seen in 155 (56.2%) patients. Lymph node and pleura are the most common extrapulmonary involvements those are seen in 53 (19.2%) and 23 (8.3%) patients, respectively.

Table 1. Clinical and demographical features

Variable	Data (n = 276)
Age (years)	41.5 ± 19.2
Gender	
Male	171 (62%)
Female	105 (38%)
Age Group	
Adult (18-64)	218 (79%)
Geriatric (65 ≥)	36 (13%)
Pediatric (< 18)	22 (8%)
Pulmonary	155 (56.2%
Extrapulmonary	108 (39.1%)
Both	13 (4.7%)

Table 2. Pulmonary and extrapulmonary involvements

Involvement	Adult (n = 218)	Geriatric (n = 36)	Pediatric (n = 22)	Total (n = 276)
Pulmonary	123	18	14	155 (56.2%)
Lymph node	38	11	4	53 (19.2%)
Pleura	20	1	2	23 (8.3%)
Bone	10	1	0	11 (4%)
Urinary	6	2	0	8 (2.9%)
Periton	5	0	0	5 (1.8%)
Miliary	4	0	0	4 (1.4%)
Gastrointestinal	2	1	1	4 (1.4%)
Skin	3	1	0	4 (1.4%)
Central Nervous System	3	0	0	3 (1.1%)
Pericardium	2	0	1	3 (1.1%)
Breast	2	1	0	3 (1.1%)

Table 3. Pulmonary and extrapulmonary involvements

Involvement	Adult (n = 218)	Geriatric (n = 36)	Pediatric (n = 22)	Total (n = 276)	*p* value
Pulmonary	123 (56.4%)	18 (50%)	14 (63.6%)	155 (56.2%)	$p > 0.05$
Extrapulmonary	84 (38.5%)	17 (47.2%)	7 (31.8%)	108 (39.1%)	$p > 0.05$
Both	11 (5.1%)	1 (2.8%)	1 (4.6%)	13 (4.7%)	$p > 0.05$

Table 4. Classification of the cases according to the diagnosis

	Adult (n = 218)	Geriatric (n = 36)	Pediatric (n = 22)	Total (n = 276)
Newly Diagnosed	186 (85.3%)	28 (77.8%)	21 (95.5%)	235 (85.1%)
Relapse	18 (8.3%)	4 (11.1%)	1 (4.5%)	23 (8.3%)
Returning after default	3 (1.3%)	0 (0%)	0 (0%)	3 (1.1%)
Transferred in	11 (5.1%)	4 (11.1%)	0 (0%)	15 (5.4%)

Number of tuberculosis patients over the years is shown in Figure 1. Presentation of pulmonary and extrapulmonary involvements over the years is shown in Figure 2. Number of the cases seems to be decreasing after 2012.

Classification of the cases according to the diagnosis is shown in Table 4. Most (85.1%) of the patients were newly diagnosed. Diagnosis method is shown in Table 5. Among the subjects, while 55.2% of them had bacteriologic diagnosis, 35.1% had histopathologic diagnosis. Two subjects died during the treatment period whereas 274 of them completed the treatment program.

Table 5. Diagnosis method

Diagnosis	Data (n = 276)
Bacteriologic	144 (52.2%)
Histopathologic	97 (35.1%)
Quantiferon	2 (0.7%)
Missing data	33 (12%)

Discussion

Tuberculosis is an infectious disease caused by Mycobacterium tuberculosis. Although tuberculosis primarily involves the lungs, any sort of extrapulmonary involvements can be seen [8-13]. Recording, analysis, and reporting the tuberculosis cases is the mainstay of the tuberculosis control program according to the WHO. As such, there is standard data set of special tuberculosis surveillance conducted in the European Region, likewise in our county [7]. In this context, we aimed to define our tuberculosis cases in our center.

The data related to tuberculosis in our county has been recruited individually according to WHO definitions since 2005. Furthermore, directly observed treatment strategy was announced in 2006. These two facts resulted in achieving more reliable data thereafter [14]. We have described the clinical involvement of tuberculosis and our results showed that most of the patients were adults (n = 123) followed by geriatric (n = 18) and pediatric (n = 13) patients. Among 276 cases, 56.2% of them had pulmonary tuberculosis whereas 39.2% (n = 108) had extrapulmonary involvements. In addition, 4.7% (n = 13) had both pulmonary and extrapulmonary tuberculosis. When compared the pulmonary and extrapulmonary involvements between the age groups, no significant difference was observed ($p > 0.05$). Up to 40% of extrapulmonary TB cases are attributable to tuberculous lymphadenitis [15]. Accounting for roughly 4% of all TB cases, pleural TB is the second leading cause of extrapulmonary TB [16].

As for the extrapulmonary tuberculosis in our study; lymph node involvement (19.2%) is the most common presentatin followed by the pleura (8.3%) and bone (4%). Previous studies reported the extrapulmonary tuberculosis rate in different populations [13,17-20]. Compared with them, extrapulmonary tuberculosis rate was higher in our study population. However, our results were consistent with the study done by İnönü *et al*. [20], and government statistics in our country. While absolute numbers have been on the rise, the prevalence of tuberculosis in relationship to population has trended downward during the past 15 years, and global public health efforts have averted an estimated 6 million deaths during this time [2]. On contrast, a decrease was observed in tuberculosis patients in our study population after 2012.

When classified the groups according to the

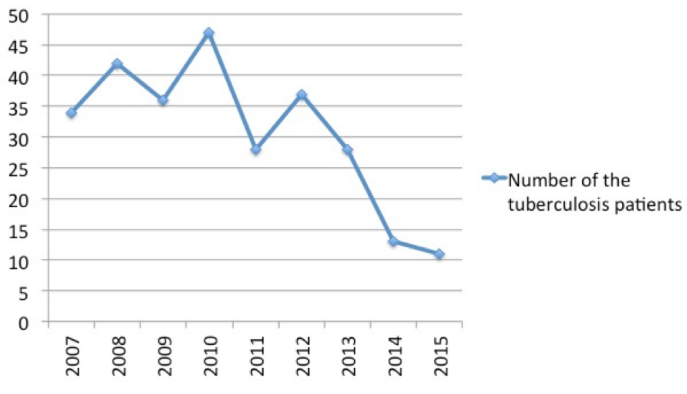

Figure 1. The number of tuberculosis patients over the years.

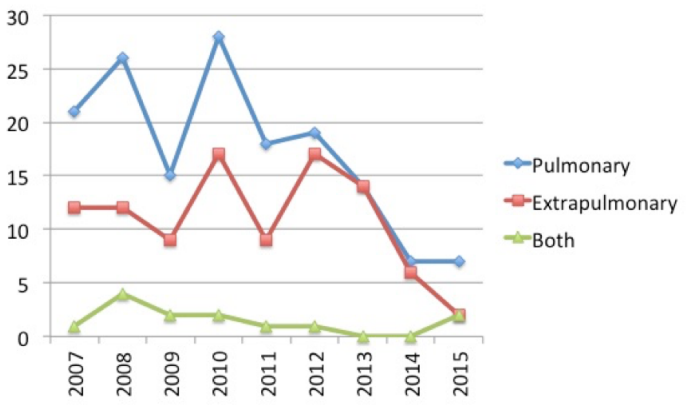

Figure 2. The number of pulmonary and extrapulmonary tuberculosis patients over the years.

diagnosis, most of them were newly diagnosed (85.1%) while relapse were seen in (8.3%) patients. Approximately 5% of the patients were transferred in our center and 1.1% was returning after default. Regarding the number of the relapse according to the age groups; although relapse rate was higher in the geriatric group, it did not reach significance. Overall, we herein imply that a possible relapse should be considered in all age groups.

Bacteriologic diagnosis is vital for the early diagnosis and directly observed treatment strategy. This fact will decrease the incidence of tuberculosis in the community. In our study, 55.2% of the subjects were diagnosed with tuberculosis according to the bacteriologic tests, and 35.1% of them according to the histopathological examination. Only two patients were diagnosed with tuberculosis with quantiferon test. However, there is missing data in twelve percent.

Limitations

We have some important drawbacks to the current study. First, our study was conducted as retrospectively. Second, this study lacks several comorbidities such as diabetes mellitus, immunosuppression, malnutrition, and malignancy those might be important for the infection of tuberculosis. Last, aside from the clinical involvement, treatment time, drug resistance, side affects were not mentioned in our study.

Conclusions

In the light of our results, tuberculosis is seen mainly in the adult age group. While pulmonary involvement is the most common presentation in all age group, lymph node and pleura involvements are the most common extrapulmonary presentations. Number of the tuberculosis seems to decrease for the recent years.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

Financing

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Synchronous and antecedent malignancies in patients with papillary thyroid carcinoma

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ABSTRACT

Objective. This study aimed to evaluate concurrently detected second primary malignancy in the patients who underwent surgery for papillary thyroid carcinoma. ***Methods***. In this study, we retrospectively analyzed the files of the patients who underwent surgery for papillary thyroid carcinoma between 2000-2017. A total number of 601 patients with papillary thyroid carcinoma were evaluated. Among these patients, 48 patients were found to have secondary primary tumors. Preoperative and postoperative laboratory examination findings of the patients were retrospectively recorded. ***Results***. Among 601 patients with papillary thyroid cancer evaluated with respect to radiation exposure, the second primary tumor with breast cancer was found to be the most common tumor. Renal cell carcinoma, malignant melanoma and stomach cancer were found to be more frequent when evaluated regardless of radiation effect. Furthermore, when molecular genetic results were evaluated, BRAF mutation rate was found to be more frequent than in other secondary tumors, especially in patients with renal cell carcinoma. ***Conclusions***. The importance of epidemiological and experimental studies of multiple cancers is obvious. Although it is known that the impact of radiation is considerable among the ones with concurrence of breast cancer and papillary thyroid carcinoma, we suggest that further studies on common molecular genetic characteristics and development of targeted treatment for detected molecules are required in the patients with renal cell carcinoma in whom papillary thyroid carcinoma is diagnosed regardless of radiation effect.radiation effect.

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Keywords: Papillary thyroid carcinoma, second primary carcinoma, carcinogenesis, renal cell carcinoma

Introduction

The incidence of papillary thyroid carcinoma has been increasing in the recent years. It constitutes about 85% of all differentiated thyroid cancers. Papillary thyroid carcinoma is a slow-growing tumor with

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favorable prognosis which is more common in women aged 20-50 years, 20-year survival rates are being around 90% [1]. Multiple primary tumors develop in the same patient at the same or different time points. The relationship between the development of multiple primary cancers and smoking is well known in humans. Nutritional deficiencies due to alcohol abuse may be an integral factor for multiple cancers. Applying radiotherapy for another cancer may also be responsible for the development of a second primary cancer. A possible explanation for the development of multiple cancers in different organs may also be a similar response to common etiological agents [2]. There are few studies in the literature on multiple malignancies with papillary thyroid carcinoma. In this study, we aimed to evaluate clinical, histopathological and molecular genetic characteristics in patients who have second primary tumor with thyroid cancer.

Methods

In this study, a total number of 601 patients with papillary thyroid carcinoma were evaluated. Among these, we retrospectively evaluated a total number of 48 cases who were diagnosed with concurrent second tumors and papillary thyroid carcinoma in our hospital between 2000-2017. All patients with concurrent tumors whose data were available were included in the study. Data on demographic features, cigarette and alcohol consumption, radiation exposure, family history and BRAF mutation status were recorded. Codon 600 (exon 15) and codon 464-469 (exon 11) mutations of the BRAF gene were examined by extracting DNA from paraffinized tissue. We defined synchronous cancers as those occurring within 6 months of the first primary cancer, while antecedent cancers were defined as those occurring more than 6 months later. Tumor types most frequently seen together with papillary thyroid carcinoma were identified. Local ethics committee approval was obtained.

Statistical Analysis

Descriptive statistics were expressed as number or percentage distributions and mininim-maximum range.

Results

A total number of 601 patients with papillary thyroid carcinoma were evaluated. Among these, 48 patients with secondary primary tumors were evaluated. The most common malignancy was breast cancer which was present in 12 patients as metachronous tumor, diagnosed within 17 years. History of radiotherapy was present in 9 of 12 patients at the breast cancer group. All patients were female (F:12/12) and the mean age was 53 years (range, 51-62 years). The average time to the diagnosis of thyroid cancer after breast cancer diagnosis was 2.9 years (min-max: 1-16 years), while it was 3.75 years (min-max: 1-16 years) after radiotherapy. Renal cell carcinoma was the most common secondary tumor when patients who received radiotherapy near the thyroid region were excluded. Besides renal cell carcinoma, malignant melanoma (4 patients), gastric cancer (3 patients), lung cancer (2 patients), parathyroid cancer (2 patients), dermatofibrosarcoma (2 patients) and lymphoma (2 patients) were also detected (Table 1).

Furthermore, colon cancer, bladder cancer, prostate cancer, basal cell carcinoma, squamous cell neck tumor, pancreas cancer, endometrium cancer, over cancer, nasopharynx cancer, malignant giant cell tumor of tendon and leukemia were all identified each in 1 patient. For all tumor types, the mean age at the

Table 1. Second primary tumor with thyroid papillary cancer cases

Type of Cancer	n	Mean Age	Gender (M/F)	Cigarette (n)	Hashimato (+)	BRAF (+)	RT
Breast cancer	12	53	0/12	6	7	1	9
Renal cell cancer	10	56	8/2	6	-	5	-
Malignant melanoma	4	64	2/2	-	-	2	-
Gastric cancer	3	62	2/1	2	-	-	-
Lymphoma	2	53	2/0	1	-	-	2
Dermatofibrosarcoma	2	57	1/1	1	-	-	-
Parathyroid cancer	2	69	0/2	1	-	-	-
Lung cancer	2	60	1/1	2	-	-	-

F = female, M = male, n = the number of patients, RT = radiotherapy

Table 2. Synchronous and antecedent malignancies in patients with papillary thyroid carcinoma

Type of Cancer	n	Synchronous (n)	Antecedent (n)
Breast cancer	12	0	12
Renal cell cancer	10	8	2
Malignant melanoma	4	2	2
Gastric cancer	3	0	3
Lymphoma	2	0	2
Dermatofibrosarcoma	2	0	2
Parathyroid cancer	2	2	0
Lung cancer	2	0	2

time of second tumor diagnosis was 56 years (min: 28, max: 76). Thyroid papillary carcinoma was determined as metachronous in 9 patients, detected within 1-16 years after the diagnosis of breast cancer. Papillary thyroid carcinoma was determined to be synchronous in 8 patients with renal cell carcinoma. Furthermore, papillary thyroid carcinoma was diagnosed in 1 patient 3 years after the diagnosis of renal cell carcinoma and papillary thyroid carcinoma was detected in 1 patient 2 years prior to the diagnosis of renal cell carcinoma (Table 2). Five patients with renal cell carcinoma were determined to be BRAF positive at molecular pathological investigation. One of these cases with micropapillary thyroid carcinoma aggressively progressed and metastasized to lymph nodes. Therefore, lymph node excision was applied. This patient died after recurrence and metastasis of renal cell carcinoma. Second patient with BRAF positivity had papillary thyroid carcinoma recurrence and wide-spread metastatic renal cell carcinoma.The second most common cancer with BRAF mutation was determined to be malignant melanoma by molecular pathology.

Discussion

Developments in the diagnosis and treatment of various malignancies and increased survival have increased the rate of secondary cancers in recent years. In one study, the rate of non-thyroid malignancy was 13.9% in the subjects with papillary thyroid carcinoma. Breast cancer, prostate cancer, malignant melanoma, leukemia and lymphoma were determined to be the most common secondary cancers, all of which were thought to be related to radiation exposure [3]. In our study, non-thyroidal malignancy rate was 7.9% among the subjects with papillary thyroid carcinoma. Breast cancer was determined to be the most common second primary tumor among the subjects with papillary thyroid cancer exposed to high levels of radiation. The possible association between breast and thyroid cancer was found to be significant with respect to radiotherapy. Early stage breast cancer is typically treated by breast conserving surgery and postoperative radiation therapy. Following treatment, breast cancer survivors are 10-50% more likely to develop a second primary breast cancer than the general population. Therefore, long-term effects of therapies such as radiation therapy among cancer survivors are important. Furthermore, the most common tumor was determined to be renal cell carcinoma independent of radiation exposure. Multiple primary tumors, developing at the same time or at different time points, have been reported to occur in 0.7%-7.7% of all carcinomas [4-6]. There are various theories on the development of multiple tumors, but the exact mechanisms are not fully understood. These theories include; “field cancerization” theory of being exposed to carcinogenic substances like alcohol and cigarette, “cancer prone” theory of having multiple tumors in different anatomical regions, and “common clonal origin” theory for explaining cases with multiple tumors by current molecular studies. In addition, underlying genetic and immunological deficiency in a patient may reflect treatment related damage or exposure to carcinogens. Long-term follow-up is important for the observation of the development of new neoplasms or the recognition of developing secondary malignancy that has been skipped before [7-17].

In our study, BRAF mutation was determined to be more frequent in renal cell carcinoma which was the most common tumor regardless of radiation. For this reason, further studies are required to detect a common genetic mutation. Multiple primer tumors are usually divided into two groups as synchronous and metachronous. We defined synchronous cancers as those occurring within 6 months of the first primary

cancer, while metachronous cancers were defined as those occurring more than 6 months later [18]. In our study, papillary thyroid carcinoma was determined to be metachronous in patients with breast cancer. In addition, it was determined to be both synchronous and metachronous in patients with renal cell carcinoma and malignant melanoma. Patients with a primary tumor have 1.29 times higher risk of a new cancer than healthy individuals [19]. Prevalence of multiple primary tumors reaches up to 36% at advanced ages [20]. According to the World Health Organization's age classification, multiple primary tumors are more common in the older age group (> 65 years). This information suggests that aging is a risk factor for the development of cancer. Immune system failure and lack of resistance to carcinogens may explain increased incidence of tumors among elderly [21]. Median age of our study subjects was 56 years (min: 28 - max: 76), being lower than WHO data. Some environmental and individual factors, such as exposure to intensive chemical carcinogens, previous treatments, genetic factors and family history could have caused this situation [22-24]. In multiple primary cancers, the likelihood of developing other cancers in the same place with primary cancer is high, called as field effect. The field effect can be summarized as cancer development in different organs due to exposure to the same carcinogenic agents or genetic alterations. This relationship was found to be statistically significant for oral cavity cancers, pharyngeal cancer, colorectal cancer and malignant melanoma in both genders. Furthermore, field effect may be relevant for women with breast and bladder cancer [25]. In our study, malignant squamous cell neck tumors and parathyroid cancers developed as a result of field effect in the patients with papillary thyroid cancer. However, the association between papillary thyroid cancer and renal cell carcinoma, which was the most common tumor regardless of radiation, requires further studies.The importance of epidemiological and experimental studies on multiple cancers is clear. Investigation of environmental factors playing role in the etiology is important for better understanding of the mechanisms of multiple cancer development. With the information obtained through such researches, development of multiple primary cancers can be minimized by defining high-risk group of patients. Probability of developing a second primary tumor is higher in the subjects with a known malignancy than in normal patients. Therefore, it is suggested that follow-up period should be long enough in the subjects treated for cancer. When multiple tumoral lesions are detected in a patient, the clinician should consider metastasis, recurrence and as well as a second primary tumor in the differential diagnosis.

Conclusions

As a result of this study, renal cell carcinoma was detected to be the most frequent malignancy in the patients with papillary thyroid carcinoma independent of radiation effect. In this respect, further work is needed to explain the link between these two tumors. This field needs further studies to explain common molecular mechanisms. In addition, higher frequency of BRAF mutation in those subjects may be important for unknown genetic mutations.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Is anemia in children with sleep disordered breathing actually a consequence of chronic disease?

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ABSTRACT

Objectives. We aimed to investigate iron metabolism and laboratory findings of anemia in children undergoing adenotonsillectomy for sleep disordered breathing. ***Methods.*** Consecutive children undergoing adenoidectomy/adenotonsillectomy for sleep disordered breathing between January 2013 and January 2015 were investigated. Routine preoperative blood tests including blood count and iron studies were analyzed. Subgroup analyses were performed addressing to the severity of sleep disordered breathing, age and duration of symptoms. Results were compared between subgroups and normal values. ***Results.*** The study included 171 children. The mean age was 5.44 ± 2.62 years. The mean hemoglobin level was 11.87 ± 1.125 gr/dL and 24 (14%) out of 171 patients had anemia (< 11 gr/dL). The mean ferritin levels were 23.23 ± 17.27 µg/L and 21.27 ± 15.44 µg/L in patients with anemia and non-anemic patients, respectively (p = 0.572). Ferritin levels decreased in only 8 (33%) out of 24 patients with anemia. The mean age, body mass index, hematocrit, mean corpuscular volume, unsaturated iron binding capacity and serum iron levels decreased in patients with anemia. The rate of anemia significantly increased in children less than or equal to 3 years of age (p = 0.020). There was no significant association between hemoglobin levels and sleep disordered breathing clinical score or duration of symptoms. ***Conclusion.*** The association between low iron status and sleep disordered breathing has previously published. Unfortunately, the type of anemia is still unclear. Our results supposed that the anemia of chronic disease secondary to chronic inflammatory process might play a role in pathogenesis of anemia in patients with sleep disordered breathing.

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Keywords: Sleep disordered breathing, adenotonsillectomy, anemia, iron deficiency, anemia of chronic disease

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Introduction

Sleep disordered breathing (SDB) is one of the most common childhood disorder with the range from simple snoring to obstructive sleep apnea (OSA) [1]. Approximately 2-3% of children are affected with SDB which may lead to behavioral, cognitive and growth abnormalities [1, 2]. The most common cause of SDB in childhood is upper airway obstruction due to adenotonsillar hypertrophy. Many hypotheses were promoted to clarify pathogenesis of adenotonsillar hypertrophy such as: allergic hypothesis, disordered lymhphoproliferation and biofilm models [3, 4]. Unfortunately, there is no enough data to explain pathogenesis of adenotonsillar hypertrophy despite these hypotheses.

SDB is associated with many co-morbid diseases which is one of the current research topic. SDB might have an impact on iron metabolism. Healthy iron metabolism has a critical importance for normal cognitive and motor development in infancy [5, 6]. Furthermore, healthy iron metabolism is essential for immune system [7, 8]. Zilberman *et al.* [9] has published the first paper addressing to association of SDB and impaired iron metabolism. They showed the iron deficiency with SDB in chronic heart failure patients. The other researchers support this finding. The improvement of day-time sleeping in patients with SDB has been published after correcting iron status and anemia [10].

The literature is indicating the increased incidence of iron deficiency in patients undergoing adenotonsillectomy [3, 11, 12]. Unfortunately, these studies mostly included patients operated for recurrent infections. Everland *et al.* [11] reported anemia rate of 56.3% in patients undergoing adenotonsillectomy because of recurrent infection and upper airway obstruction. Kerstein *et al.* [13] evaluated the iron status of children diagnosed with SDB undergoing adenotonsillectomy. They reported low iron status in particular children under 6 years of age. This study concluded the low impaired iron status as an iron deficiency anemia. However, this impaired iron metabolism might be associated with chronic inflammatory process accompanied to SDB. The literature is supporting the increased pro-inflammatory cytokines (IL-6, THF–α, C reactive protein) and decreases IL-10 which is an anti-inflammatory cytokine [14-17]. Iron deficiency anemia is associated with low hemoglobin (Hb), hematocrit (Hct), mean corpuscular volume (MCV), serum iron level and serum ferritin levels. But, anemia of chronic disease is associated with low serum iron, iron binding capacity and normal or high ferritin levels [18]. Ferritin is a positive acute phase reactant that explains the normal or high ferritin levels in anemia of chronic disease. Everland *et al.* [11] reported normal ferritin levels in 57% of children with anemia that is not surprising.

We analyzed the iron metabolism and effects of SDB in patients undergoing adenotonsillectomy for upper airway obstruction.

Methods

A retrospective clinical trial was conducted in an academic tertiary referral center between January 2013 and January 2015 after obtaining local Medical Ethics Committee approval. A total of 186 adenoidectomy, tonsillectomy and adenotonsillectomy case files were reviewed retrospectively and subjects were included in the study if they operated for SDB. Patients were excluded from the study if they met any of following: 1) nasal septal deviation, 2) history of recurrent tonsillitis, 3) history of anemia treatment in the past 3 months, 4) the other causes of anemia; recurrent epistaxis, bleeding disorders, surgical operations in the past 3 months, 5) history of chronic diseases.

We use a standard questionnaire for SDB preoperatively that include; mouth breathing during sleep, daytime mouth breathing, apnea, snoring, cough, rhinorrhea and restless sleep. Scoring is used for each of above; 0: never, 1: occasionally, 2: frequently and 3: always [19, 20]. Patients were categorized into 3 subgroups according to these questionnaire score; mild: 1-7, moderate: 8-14 and severe: 15-21. Age groups were conducted as ≤ 3 years, >3 years - ≤ 6 years and > 6 years of age. Duration of primary symptoms were categorized as ≤ 12 months, > 12 months - ≤ 24 months and > 24 months.

All patients were analyzed for Hb, Hct, MCV, ferritin, unsaturated iron binding capacity, serum iron, aPTT and INR. Results were compared to the World Health Organizations (WHO) normal range.

Statistical Analysis

Continuous data were summarized as mean ± standard deviation and categorical data were presented as frequency and percent. Distribution of continuous variables were controlled with Shapiro-Wilks test.

Comparisons for continuous variables were done using independent samples t test for two groups and one-way ANOVA followed by Tukey HSD post hoc test for three and more groups. Categorical data were analyzed by Pearson chi-square or Fisher's exact tests. Statistical analyses were performed with SPSS v.23 statistical package and statistical significance level was considered as $\alpha = 0.05$.

Results

One hundred and eighty patients undergoing adenoidectomy, tonsillectomy, adenotonsillectomy for SDB were analyzed. The study included 171 patients with sufficient laboratory data. The mean age was 5.44 ± 2.62 years. Tonsilla platina size was assessed by using the Brodsky grading scale [21]. The adenoid tissue volume was graded from 1 to 4 with flexible endoscopy findings depending on choanal opening [22].

The mean Hb level was 11.87 ± 1.125 gr/dL and 24 (14%) out of 171 patients had anemia (Hb < 11 gr/dL). The mean ferritin level was 22.28 ± 17.16 µg/L. Forty-seven (27%) patients had low ferritin levels (< 16 µg/L). The mean age ($p < 0.001$), BMI ($p = 0.021$), Hct ($p < 0.001$), MCV ($p = 0.013$) and serum iron ($p = 0.038$) levels was lower in patients with anemia. Unsaturated iron binding capacity level was lower in anemia patients but the difference was not statistically significant. Table 1 summarizes the laboratory findings in patients with anemia and normal Hb levels. Ferritin levels were decreased in only 8 (33%) patients with anemia. Furthermore, the mean ferritin levels were 23.23 ± 17.27 µg/L and 21.27 ± 15.44 µg/L in patients with anemia and non-anemic patients respectively. The increased ferritin levels in patients with anemia documented but the difference was not statistical significant (Table 1).

Table 2 summarizes the demographics according to SDB severity. There were 7 (3%) patients in mild SDB, 91 (49%) patients in moderate SDB and 88 (48%) patients in severe SDB groups. The mean ages were 5.86 ± 1.49 years, 5.91 ± 2.77 years and 4.93 ±

Table 1. Comparison of anemic and non-anemic patients

	Hb < 11 g/dL (n = 24)	**Hb ≥ 11 g/dL (n = 147)**	***p***
BMI	15.96 ± 1.74	17.04 ± 2.77	**0.021**
Mean age (year)	4.00 ± 1.84	5.69 ± 2.68	**< 0.001**
Ferritin µg/L	23.23 ± 17.27	21.27 ± 15.44	0.572
Hct (%)	33.12 ± 4.46	38.45 ± 2.17	**< 0.001**
MCV (fL)	74.25 ± 10.33	79.94 ± 3.75	**0.013**
UIBC (µmol/L)	236.27 ± 90.04	259.82 ± 64.79	0.145
SI (µmol/L)	53.59 ± 29.13	67.39 ± 28.20	**0.038**

BMI = body mass index, Hb = hemoglobin, Hct = hematocrit, MCV = mean corpuscular volume, SI = serum iron, UIBC = unsaturated iron binding capacity

Table 2. Demographics according to severity of SDB

	Mild (0-7) (n = 7)	**Moderate (8-14) (n = 91)**	**Severe (15-21) (n = 88)**	***p***	**General**
Mean age (year)	5.86 ± 1.49	5.91 ± 2.77	4.93 ± 2.44	**0.038**	5.44 ± 2.62
≤ 3 years	0 (0.0%)	19 (20.9%)	30 (34.1%)		49 (26.3%)
> 3 - ≤ 6 years	6 (85.7%)	34 (37.4%)	37 (42.0%)	**0.013**	77 (41.4%)
> 6 years	1 (14.3%)	38 (41.8%)	21 (23.9%)		60 (32.3%)
Female	5 (71.4%)	44 (48.4%)	44 (50.0%)	0.570	93 (50.0%)
Male	2 (28.6%)	47 (51.6%)	44 (50.0%)		93 (50.0%)
Duration of symptoms	14.29 ± 9.98	25.15 ± 17.97	23.76 ± 14.90	0.233	24.09 ± 16.40

SDB = sleep disordered breathing

Table 3. Laboratory findings in comparison with severity of SDB

	Mild (0-7) (n = 7)	Moderate (8-14) (n = 84)	Severe (15-21) (n = 80)	*p*
Hb < 11 g/dL	0 (0.0%)	13 (15.7%)	11 (13.6%)	0.524
Ferritin < 16 µg/L	1 (16.7%)	23 (27.3%)	23 (28.75%)	0.713
Hct (%)	37.04 ± 1.85	37.86 ± 3.86	37.59 ± 2.46	0.736
MCV (fL)	82.16 ± 2.41	78.96 ± 6.42	79.07 ± 4.62	0.337
UIBC (µmol/L)	216.00 ± 65.61	250.75 ± 62.76	263.64 ± 75.98	0.239
SI (µmol/L)	82.60 ± 50.30	71.31 ± 27.88	57.78 ± 24.92	**0.007**

Hb = hemoglobin, Hct = hematocrit, MCV = mean corpuscular volume, SDB = sleep disordered breathing, SI = serum iron, UIBC = unsaturated iron binding capacity

Table 4. Laboratory findings in comparison with age groups

	≤ 3 years (n = 41)	> 3 - ≤ 6 years (n = 76)	> 6 years (n = 54)	*p*
Hb < 11 g/dL	11 (26.8%)	9 (11.8%)	4 (7.4%)	**0.020**
Ferritin < 16 µg/L	14 (34.1%)	27 (35.1%)	6 (10.9%)	**0.005**
Hct (%)	35.88 ± 4.29	37.74 ± 2.60	39.02 ± 2.24	**< 0.001**
MCV (fL)	76.72 ± 8.15	79.36 ± 3.46	80.68 ± 4.86	**0.002**
UIBC (µmol/L)	260.28 ± 70.32	258.22 ± 70.77	247.40 ± 67.02	0.630
SI (µmol/L)	58.23 ± 23.31	67.49 ± 30.75	69.77 ± 28.24	0.139

Hb = hemoglobin, Hct = hematocrit, MCV = mean corpuscular volume, SI = serum iron, UIBC = unsaturated iron binding capacity

2.44 years in the mild, moderate and severe SDB groups, respectively ($p = 0.038$). The mean age in the severe group was significantly lower than in the mild and moderate group. All patients with anemia were in moderate and severe SDB groups but Hb, Hct, MCV, ferritin, and unsaturated iron binding capacity were not significantly different in these subgroups (Table 3). Serum iron was significantly difference among SDB groups ($p = 0.007$). When we categorize the patients depending on apnea score, as low apnea score (0 or 1) and high apnea score (2 or 3), there were 96 patients with low apnea score and 75 patients with high apnea score. The anemia rates (Hb < 11 g/dL) between the low and high apnea score groups were not different, 11.5% and 17.3%, respectively ($p = 0.272$). However, lower ferritin rate (Ferritin < 16 µg/L) was 20.0% in low apnea score group and 37.0% in high apnea score group, and the difference was statistically significant ($p = 0.013$). The other questionnaires were not significantly associated with anemia when analyzed each of them.

Table 4 summarizes the subgroups according to age. Hb, Hct, MCV and ferritin levels were significantly decreased in small age group (≤ 3 years of age). The anemia rates (Hb < 11 g/dL) between the ≤ 3years of age and > 6 years of age groups were different, while the > 3 - ≤ 6 years of age group was similar to them. The lower ferritin rates (Ferritin < 16 µg/L) in the ≤ 3 years of age and > 3 - ≤ 6 years of age groups were higher than in the > 6 years of age group. The mean of Hct rates were different in all groups while MCV level in small age group was significantly lower than in the other age groups. There was no significant association for Hb, MCV, serum iron, unsaturated iron binding capacity level and ferritin levels according to duration of symptoms (Table 5). Hct levels were significantly increased in patients with extended duration of symptoms ($p = 0.042$).

Discussion

SDB is a common health problem in children with the estimated incidence of 2-3%. SDB may lead to numerous morbidities such as neurocognitive disorders, craniofacial growth abnormalities, enuresis and cardiovascular problems if not treated [1]. The

Table 5. Laboratory findings in comparison with duration of symptoms

	< 12 months (n = 72)	12-24 months (n = 49)	> 24 months (n = 50)	*p*
Hb < 11 g/dL	10 (13.9%)	9 (18.4%)	5 (10.0%)	0.487
Ferritin < 16 µg/L	17 (23.0%)	18 (37.5%)	12 (23.5%)	0.229
Hct (%)	37.13 ± 3.47	37.62 ± 3.07	38.60 ± 2.73	**0.042**
MCV (fL)	79.12 ± 6.06	78.30 ± 6.22	80.02 ± 3.64	0.302
UIBC (µmol/L)	260.03 ± 62.02	249.89 ± 77.43	252.51 ± 73.01	0.739
SI (µmol/L)	61.26 ± 27.43	69.13 ± 34.40	69.83 ± 22.26	0.217

Hb = hemoglobin, Hct = hematocrit, MCV = mean corpuscular volume, SI = serum iron, UIBC = unsaturated iron binding capacity

impaired iron metabolism is the other effect of SDB. The published literature documented the increased incidence of anemia in patients underwent adenotonsillectomy [3, 12, 13] and improved anemia after operations without any iron supplementation [11]. Unfortunately, there is no enough data to explain pathogenesis of impaired iron metabolism in these patients. There are two potential causes of impaired iron metabolism in SDB; nutritional iron deficiency and anemia of chronic disease secondary to chronic inflammation. Iron deficiency is the commonest nutritional deficiency worldwide according to WHO and affects a significant part of the population [23]. WHO estimates iron deficiency in 2.5% of pediatric population and describes an abnormality if the rate more than 5% [24]. The evaluation iron deficiency starts with measurement of Hb and Hct levels that are non-specific markers. Ferritin, serum iron, total iron binding capacity or unsaturated iron binding capacity are widely used for differential diagnosis and confirmation of iron deficiency. The decreased Hb (< 11 g/dL) and ferritin (< 16 µg/L) levels are important for diagnosis of iron deficiency anemia. Anemia of chronic disease is an iron metabolism disorder that might be associated with neoplastic diseases, chronic immunologic diseases, chronic inflammation and trauma [18]. The main mechanism of anemia of chronic disease is depending on increased levels of IL-1, IL-6, TNF-α and CRP. These cytokines affect the erythropoietin synthesis from kidney that results with decreased erythropoiesis and decreased iron absorption from gastrointestinal system [25]. The increased releasing of Hepsidin in chronic inflammatory process plays an important role of decreased iron absorption from intestine. Patients have normochromic normocytic anemia in early stages that progress to hypochromic microcytic anemia. Ferritin levels might be normal or increased in these patients, which is an acute phase reactant. Unsaturated iron binding capacity or total iron binding capacity levels were decreased with serum iron. These findings are crucial to differentiate anemia of chronic disease and iron deficiency anemia.

The increased levels of TNF-α, IL-6 and CRP have been reported in patients with OSA [14-16]. The decreased IL-10 levels in non-obese children with OSA was documented that corrected after adenotonsillectomy [17]. IL-10 is an anti-inflammatory cytokine which is negative correlated with OSA severity [26].

We documented anemia (Hb < 11 g/dL) rate in 14% of those patients underwent adenotonsillectomy for SDB. This rate is much more than WHO expectations (2.5%) which is abnormal. Hct, MCV, serum iron and unsaturated iron binding capacity were significantly decreased in patients with anemia. However, only 8 (33%) patients had low ferritin levels in patients with anemia. Additional, 16 (67%) of those patients with anemia had normal ferritin levels. The mean ferritin levels were 23.23 ± 17.27 and 21.27 ± 15.44 µg/L in patients with anemia and non-anemic patients, respectively (Table 1). These findings are supporting the role of inflammatory process in anemia. Louise *et al.* [27] analyzed the association of ferritin with OSA in adults. They did not find an association between apnea-hypopnea index and ferritin levels but they documented the negative correlation between apnea-hypopnea index and ferritin levels in only women patients. The same study is indicating the association of lower minimum oxygen saturation and increased sleep stage shifts (that are correlated with severity of OSA) with increased ferritin levels. There are many publications supporting the chronic inflammatory process and increased ferritin levels in

patients with OSA [28-31]. In our study, all patients with anemia had moderate or severe SDB clinical score (Table 3) but the difference was not significant. Everland *et al.* [11] reported the 57% normal ferritin levels of those patients underwent adenotonsillectomy because of recurrent infection and upper airway obstruction. They indicated the role of chronic inflammatory process in these increased ferritin levels. Unfortunately, they did not do subgroup analysis addressing to the indication of adenotonsillectomy. We include only patients underwent adenotonsillectomy for SDB in the current study. On the other hand, Elverland *et al.* [11] reported the corrected Hb levels and iron metabolism at postoperative 6th month. This result is an important characteristic of anemia of chronic disease. Iron metabolism immediately becomes normal levels when you correct the underlying disease [25]. Chronic inflammation is the main cause of anemia in these patients that corrected after adenotonsillectomy.

Kerstein *et al.* [13] reviewed 94 children undergoing adenotonsillectomy. They categorized the study population according to age; Group A: 0-2 years, Group B: 2-6 years, Group C: above 6 years. They reported 18 % anemia rate (17 patients) in this study population. Of those 17 patients, anemia rate was significantly increased in Group A. We report the increased anemia rate in children under 3 years of age that correlated with Kerstein *et al.* [13]. Although iron requirement decreases progressively after the sixth month of life until 3 years [25], the high rate of anemia in this age group SDB patients suggests that small patients may be more affected by inflammation. Bitar *et al.* [20] reported the increased SDB score in patients under 3 year-olds that indicates children under 3 year-olds were much affected than older children [20]. Children under 3 years of age might be influenced from SDB much more than older children according to our results. SDB clinical score, in the current study, was increased in children under 3 years of age that supports SDB severity in this cohort. Thirty out of 49 children less than 3 years of age had severe SDB clinical score (Table 2). Kerstein *et al.* [13] analyzed the results depending on the mean values of each of subgroups. They reported hypochromic (MCH < 27 pg) and microcytic (MCV < 76 fL) mean values in children under 2 year-olds. The other subgroups had low-normal mean values. Unfortunately, they did not compare the mean values of 17 patients with anemia and non-anemic patients. It is not possible to clarify type of anemia without evaluation of anemic patients. We found significantly decreased Hct, MCV, serum iron and unsaturated iron binding capacity levels in patients with anemia in comparison with non-anemic patients. Additional, only 8 (33%) out of 24 patients had low ferritin levels (Table 1). These findings support an impaired iron metabolism secondary to inflammation.

The Limitations of the Study

This is a retrospective observational study which is the main limitation of paper. We did not have a control group. Additional, we were not able to analyze inflammatory markers owing to the retrospective setting. It would be better if we had inflammatory markers and cytokine levels. Polysomnography test is a gold standard test to evaluate SDB that supports objective results. Unfortunately, we do not use polysomnography as a routine test for evaluation of SDB; we use a questionnaire. We could have used subset analysis if we had polysomnography test results.

Conclusions

SDB is an important health problem in children that may result in many behaviors or growth problem. Unfortunately, there is no enough data about iron metabolism in pediatric SDB patients. Anemia in SDB might be result of iron deficiency or chronic inflammatory process.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Primary cardiac B cell lymphoma

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ABSTRACT

Primary tumors of the heart are very uncommon and approximately 25% of them are malign. Primary cardiac lymphomas account for approximately 4% of the primary cardiac tumors. Both B- and T-cell lymphomas have been reported. We report the case of a 75-year-old male who was referred to our hospital complaining of fatigue, dyspnea and swelling in the abdomen. Transthoracic echocardiography revealed a mobile 5.0×4.3 cm mass in the right atrial cavity impinging tricuspid valve. Surgery was performed and the mass was resected. The pathological and histological examination of the removed mass showed diffuse large B-cell lymphoma.

Eur Res J 2018;4(3):227-230

Keywords: Cardiac tumor, malignancy, right atrium, lymphoma

Introduction

Primary cardiac lymphomas (PCLs) (which, by definition, arise from the heart and/or the pericardium without evidence of extracardiac involvement) are extremely rare and account for about 1% of the primary cardiac tumors and 0.5% of the extranodal lymphomas [1, 2]. Therewithal, disseminated lymphoma with cardiac involvement can occur in up to 20% of patients with lymphoma [2]. Recently, the incidence of PCLs has been increasing since they have been diagnosed as a manifestation of immunodeficiency states and with the help of multiple diagnostic modalities have been developed. Clinical and anatomic features of PCL remain uncertain. There is no standardized therapy for PCL. Tumor resection and standard chemotherapy combination regimens are widely used as therapeutic modality. In this article, we report a 75-year-old man with large cardiac mass who was diagnosed primary cardiac extranodal diffuse large B cell lymphoma.

Case Presentation

A 75-year-old immunocompetent man with coronary artery disease medical history presented a 1-month history of dyspnea on exertion, shortness of breath and swelling in the abdomen. An electrocardiogram revealed sinus rhythm without any feature of myocardial ischemia. Transthoracic echocardiography disclosed a large intracardiac mass (5.0×4.3 cm), which extended from the right atrium, impinging tricuspid valve, a moderate pericardial effusion, and a preserved ejection fraction (Figure 1A). After then, the patient underwent transesophageal

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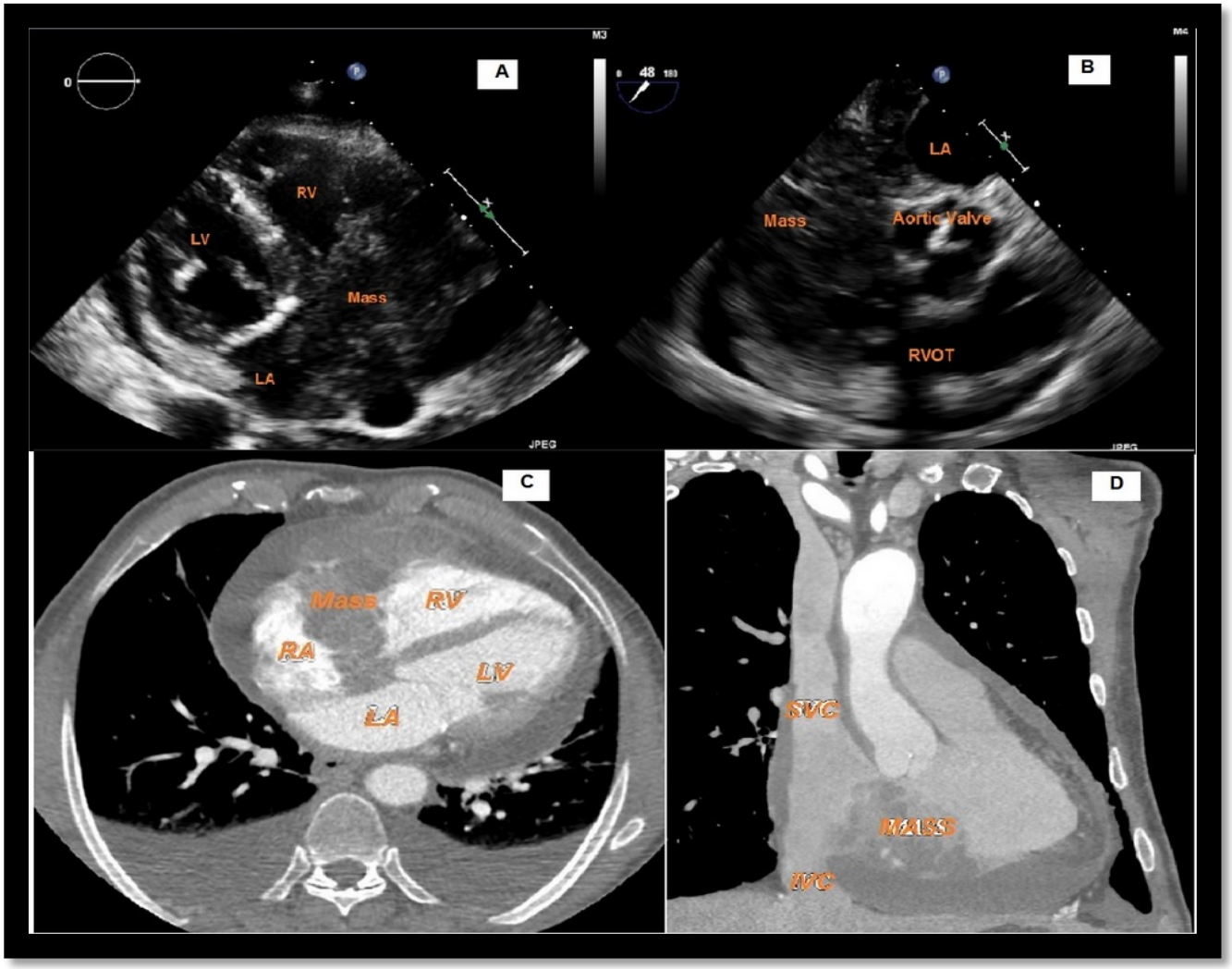

Figure 1. Modified apical four chamber (A) and short axis (B) echocardiographic view showing right atrial mass; transverse (C) and sagittal plane (D) of tomographic view showing cardiac mass. IVC = inferior vena cava, LA = left atrium, LV = left ventricle, RA = right atrium, RV = right ventricle, RVOT = right ventricular outflow tract, SVC = superior vena cava

echocardiography which confirmed the mass, arising from the right atrium, associated invasion of the right ventricle and the interatrial septum, showed causing mild tricuspid valve obstruction and a moderate pericardial effusion (Figure 1B). A contrast cardiac computed tomography (CT) showed a large infiltrating mass (11×7×4.5 cm sized), localized in the right atrium, arising from posteroinferior wall of the right atrium and diffuse infiltration of almost the full of the right atrium, contiguous to the right ventricle, extending to the pericardium from lateral wall of the right atrium, giving early and delayed heterogeneous contrast enhancement and involving the proximal segment of right coronary artery (Figure 1C and 1D). Presence of extracardiac involvement was excluded with the global assessment of the chest and abdomen with CT and scintigraphy. This case was discussed in the multidisciplinary meeting and decided for resection of the mass, because of mechanical complication as tricuspid valve stenosis. A median sternotomy was performed, the mass was excised with the use of cardiopulmonary bypass with moderate systemic hypothermia, deep topical hypothermia, and cardioplegic cardiac arrest. A right atriotomy was employed for resection of mass. Right heart mass was partially resected. Right atrial mass was resected however the right ventricular mass resected partially because the mass has completely invaded the right ventricular free wall. The tricuspid valve was normal function and had not mass invasion, so that tricuspid valve was protected. The pathologic examination of removed cardiac mass had reported as below after immunohistochemistry study: intense cytoplasmic staining with LCA(+), CD79a(+) and Bcl-2(+), intense membranous staining with CD20 (+), nuclear staining in 40-60 % with Bcl-6(+) and focal staining with Vimentin(+) and CD5(+) (Figure 2). Staining with CK19, CD31, CD10, Cyclin D1(Bcl-1), EMA, CD21

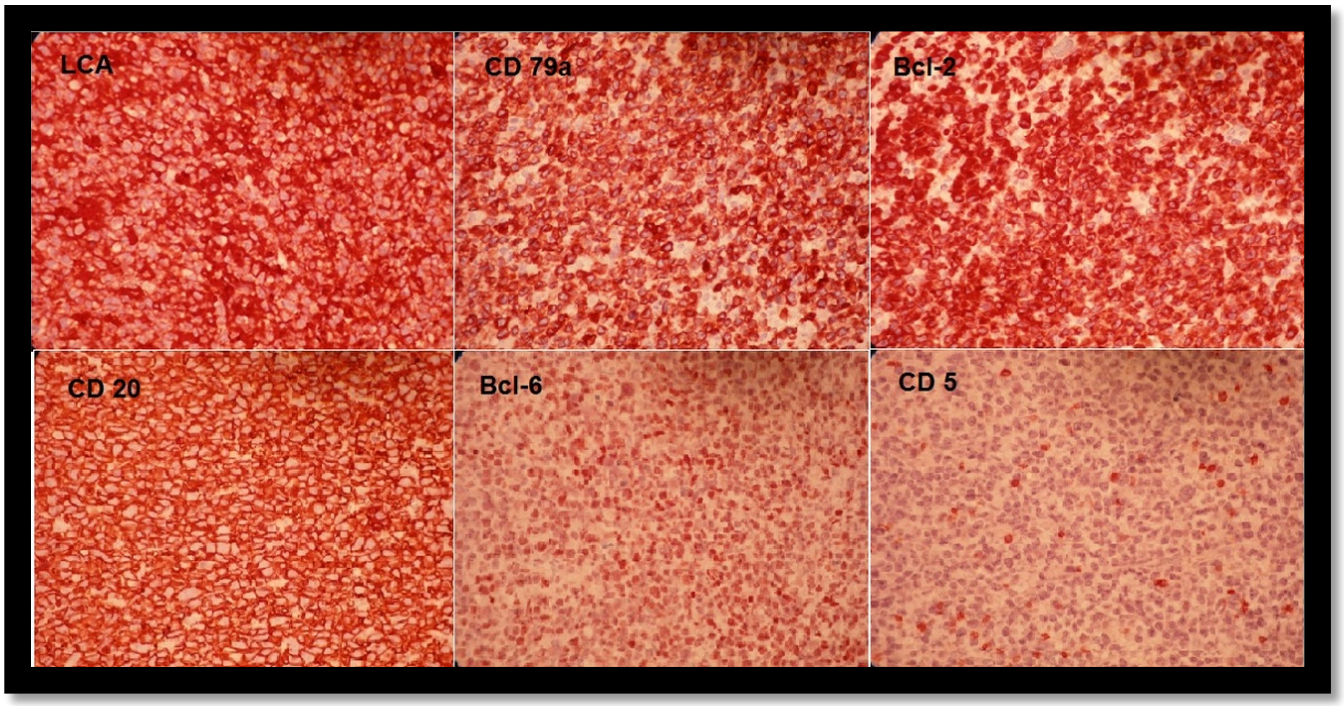

Figure 2. In the immunohistochemical study, proliferating cells were stained diffuse cytoplasmic with LCA, CD79a and Bcl-2, stained diffuse membranous with CD20, stained nuclear with Bcl-6 and stained focal with CD5.

and CD30 were not demonstrated. In the light of immunohistochemistry evaluation, the final pathologic report confirmed the diagnosis of diffuse large B cell lymphoma. We planned consulting with hematology service for chemotherapy. Unfortunately, the patient died at postoperative 7th day due to post-surgical cardiac complications.

Discussion

PCLs are extremely rare and primary lesion arises from the heart or the pericardium. Therewithal, myocardial or pericardial invasion of systemic lymphomas could be seen in up to 20% along the course of the disease [3]. The most common sub-type of PCL was diffuse large B-cell lymphomas and PCL are mostly right-side involvement [4]. The fundamental characteristics of PCL included clinical, imaging and pathologic features, diagnosis and treatment strategies remain being challenging. PCL patients present different and non-specific symptoms such as dyspnea, edema, arrhythmia, cardiac tamponade, palpitations and heart failure [5]. In our case most relevant symptom was dyspnea. Most of available literature about PCL consist of case reports [6]. Carras *et al.* [3] reported on the largest monocentric series of patients with PCL analyzed from initial symptoms to pathological diagnosis and treatment with chemotherapy. They examined a total of 13 patients. No patient was immunocompromised. Lymphoma aroused from the right atrium at 10 patients (77%). They made pathological diagnosis (diffuse large B-cell lymphoma in 12 cases and Burkitt in 1 case) on cardiac surgical biopsies and by intravascular procedure. All patients received first-line chemotherapy and complete response rate was 62%. Recurrences occurred in 55% of patients, mostly at extracardiac extranodal sites. During 1975-2017, only 249 cases of PCL were reported in the literature. Diffuse large B-cell lymphoma is the most common sub-type of PCL; the remaining sub-types include Burkitt's lymphoma, T-cell lymphoma, small lymphocytic lymphoma and plasmablastic lymphoma [4]. Unfortunately, at present, no definite guidelines for the management of PCL. Complete surgical resection of PCL provides no survival benefit. Early systemic chemotherapy appears to be the only effective therapy. The major regimen is the same as that for other types of non-Hodgkin lymphoma, namely cyclophosphamide/ hydroxydaunorubicin/ oncovin/ prednisone (CHOP) and since 2001, CHOP + rituximab. General response rate of patients with PCL to chemotherapy is 79% and the complete remission rate is 59%. The median overall survival of patients with PCL is associated with poor prognosis [4].

Transesophageal echocardiography is the firstly choice diagnosis tool for PCL. Transthoracic and transesophageal echocardiography have a sensitivity of 55-60% and 97-100%, respectively for primary cardiac tumors. Cardiac magnetic resonance imaging is superior to CT which are enhanced techniques visualize morphology and tumor localization [6]. Usually location of PCL is atrial and infiltrating to atrial or ventricular walls. The earliest sign of PCL can be sometimes pericardial thickening and effusion which is also commonly seen in other diseases [7].

Definite diagnosis of PCL is biopsy of cardiac mass. Biopsy can be taken by intracardiac or surgically. Patients with pericardial effusion, cytological analysis of pericardial fluid also make the diagnosis. Treatment is usually chemotherapy with combining surgery if necessary. Surgery alone has no effect outcome [8]. Surgery can enable time for chemotherapy and resolve hemodynamics problems due to obstructions [9].

Conclusions

Although PCL is associated with poor prognosis and life-threatening complications, we believe that, timely and appropriate treatment can be beneficial, and more effective treatment options will update with clinical therapeutic regimens.

Informed consent

Written informed consent was obtained from the patient's family for the publication of this case report.

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Neutropenic enterocolitis and colonic perforation in a patient with breast carcinoma treated with taxane-based chemotherapy: a case report and review of the literature

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;ABSTRACT

Neutropenic enterocolitis or typhlitis is one of the rare but high mortality acute complications of neutropenia that develops in immunosuppressed patients due to chemotherapy. It is a segmental cecal and ascending colon inflammation that can progress to necrosis and perforation. Although it is mostly observed in myelosuppressed and immunosuppressed patients, like those who have leukemia and lymphoma, it can also be observed in malignancies treated with myelosuppressive chemotherapy. It has been reported particularly in patients with solid tumors treated with taxane-based chemotherapy. In this article, a 40-year-old patient with invasive ductal breast carcinoma is presented, who was diagnosed with neutropenic enterocolitis and colonic perforation that developed 6 days after chemotherapy (Docetaxel 75 mg/m^2 and cyclophosphamide 600 mg/m^2). If neutropenic fever, abdominal pain, abdominal distension, and tenderness develops in a patient under taxane-based chemotherapy, neutropenic enterocolitis is a condition that must definitely be considered. It should be noted that it is possible to reduce mortality and morbidity by means of appropriate antibiotics and a timely surgical intervention.

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Keywords: neutropenic enterocolitis, typhlitis, taxane-based chemotherapy

Introduction

Neutropenic enterocolitis (NE) or typhilitis is a serious complication of neutropenia characterized by segmental ulceration or inflammation with necrosis of ileum, caecum and ascending colon. It may be complicated with perforation and septicemia. It also appears as a complication of neutropenia that develops mostly in leukemia and lymphoma patients [1]. NE has also been identified in patients with solid tumors treated with new chemotherapeutic drugs and intensive immunosuppressive therapy [2]. It has been reported particularly in patients with solid tumors treated with taxane-based chemotherapy [3-8]. The clinical features consist of fever, watery diarrhea, and crampy abdominal pains, which are typical and not

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specific to the disease. Reported mortality rate is 21% to 48%. When complications such as bleeding and perforation develop, surgical intervention should be applied without delay [1]. In this article, a case of breast cancer in which neutropenic enterocolitis and colonic perforation developed after docetaxel treatment, is presented.

Case Presentation

A 40-year-old female had undergone mastectomy two years ago, due to the diagnosis of ductal carcinoma in situ (DCIS), and then lesion developed under the flap. Pathological examination revealed invasive ductal carcinoma, and estrogen receptor was found to be 100% positive, while progesterone receptor and c-erb B2 were negative. The patient was admitted with abdominal pain to the hospital and was hospitalized. Six days before her admission, the patient had received a treatment involving docetaxel 75 mg/m^2 and cyclophosphamide 600 mg/m^2. In her physical examination fever was determined to be 37^{0}C (tympanic), her pulse was 120/minute, her blood pressure was 120/60 mmHg, and her respiratory rate was 19/minute. There was a minimal epigastric tenderness with deep palpation during the abdominal examination, peritoneal irritation was not detected. The laboratory studies revealed; leukocyte: 820/mm^3 (absolute neutrophil count: 150/mm^3), hemoglobin: 13.1 g/L, and platelet: 271.000/mm^3. The routine biochemical values were normal. No features that could explain the acute abdominal condition was found in any abdominal ultrasonography. Filgrastim 48MU was administered to the patient due to neutropenia. On the 9th day of her follow-up period, her fever was found to be 39^{0}C. Physical examination revealed abdominal guarding and rebound tenderness. C-reactive protein was 237 mg/L (normal range: 0-5 mg/L), the leukocyte count was 27.000/mm^3, and the absolute neutrophil count was 25.000/mm^3. The patient was consulted with infectious diseases. With the computerized tomography (CT) of the abdomen, wall thickening, and widespread abdominopelvic peritoneal fluid were found in the ascending colon, and most significantly in the caecum. In two localizations of the lower part of the caecum, the loss of wall continuity and neighboring peritoneal free air signs were found to be compatible with neutropenic enterocolitis (Figure 1). Oral intake of the patient was stopped, and intravenous hydration was initiated. With the prediagnosis of NE, meropenem (3×1gr, IV) and metronidazole (3×500mg, IV) was administered to the patient.

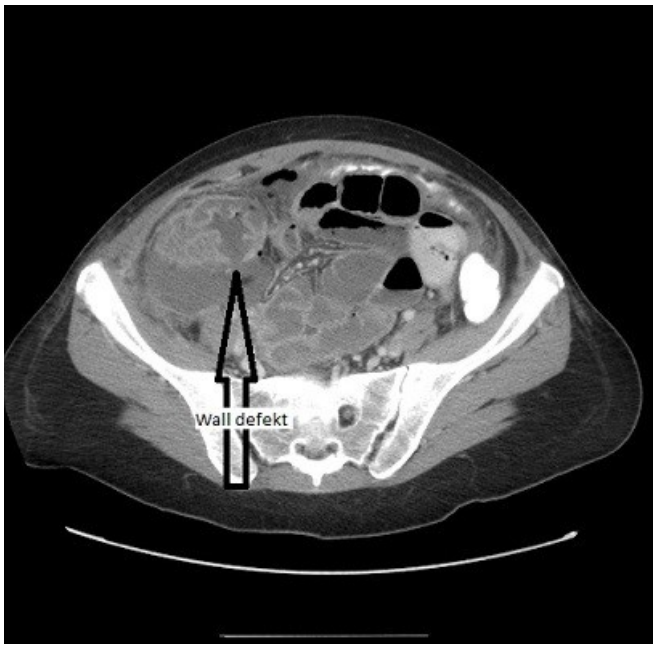

Figure 1. There is thickening of colon wall at ascendant colon, and it is most apparent at cecum as well diffuse ascites is seen most apparent at pericecal area. There is an area that the continuity of the colonic wall cannot be seen at proximal cecum near appendiceal root (arrow), and free air particles are also shown.

The general condition of the patient deteriorated, tachycardia and signs of peritoneal irritations developed. The patient was operated due to acute abdomen; cecal perforation was repaired and ileostomy was performed. No fever and abdominal pain developed after the operation and the patient was discharged on the 7th postoperative day. Additional doses of docetaxel were decided to be administered.

Discussion

Neutropenic enterocolitis is an intestinal inflammation rarely seen in cancer patients after chemotherapy. It is characterized by segmental ulceration of ileum, caecum and ascending colon as well as their inflammation with necrosis [1]. Clinically, certain initial symptoms can be observed such as fever, abdominal pain, nausea, vomiting, watery diarrhea that may sometimes leads to bleeding and polymicrobial sepsis. Abdominal rebound and defense can commonly be seen usually in the right upper quadrant, and sometimes in all quadrants;

however, it may not be detected in patients using steroids [7]. Similar clinical characteristics may also be observed in some other conditions such as appendicitis, Clostridium difficile colitis, intestinal invagination, ileus caused by vincristine, pancreatitis due to L-asparaginase, drug-induced cholestasis and cholecystitis, and fungal infections. Its pathogenesis is not fully known. It is most commonly observed after hematologic malignancies such as leukemia and lymphoma; however, it has been reported to be seen in patients with solid tumors treated with new chemotherapeutics and intensive chemotherapy [1, 2-10].

The agents most commonly associated with neutropenic enterocolitis are cytosine arabinoside, etoposide, and daunorubicin. Other influential agents include doxorubicin, methotrexate, vincristine, taxane-based chemotherapeutic agents, cyclophosphamide, and prednisone [2, 7, 9]. NE that developing after standard dose combination chemotherapy with nedaplatin and irinotecan for testicular tumor was reported by Takaoka *et al.* [2] for the first time. A search of the PubMed English literature between years 1993-2017 revealed NE cases developing taxane-based chemotherapy [3-8, 10]. Such complications can be observed in 0.1% of taxane-based chemotherapies [8]. In 1993, Seewaldt *et al.* [4] first reported an intestinal perforation that developed after paclitaxel therapy in an ovarian cancer patient. As in our case, there are five cases with NE that developing after the use of paclitaxel in the treatment of breast cancer [3, 5-8] (Table 1).

Symptoms usually observed within 10 to14 days after chemotherapy, when neutropenia is most obvious [7]. It is noticed that NE developed usually after 6-10th day of the chemotherapy. [3, 5-7]. In our case, NE developed on the 6th day after the first cycle. As in our case, all these cases of breast cancer, in which NE developed, taxane-based chemotherapy drugs have been used in combination with other chemotherapeutic agents (Doxorubicin, Cyclophosphamide, Epirubicin, 5% Fluorouracil) [3, 5-7].

CT and ultrasound (US) are the radiological methods used for diagnosis. It is likely to observe thickening of the intestinal wall, inflammatory mass in the right lower quadrant, caecum enlargement, pericaecal fluid, and inflammatory changes in the pericaecal tissue [7, 8]. CT is the most preferred

Table1. Summary of reported cases of neutropenic enterocolitis associated with docetaxel

Authors	Cancer	Patient	Chemotherapy regimen	Date of onset of symptoms	Symptoms	Outcome
Ramsing *et al.* [3]	Breast cancer	66-year-old, female	Docetaxel Cyclophosphamide	7th day of chemotherapy	Generalized abdominal pain, fever, rigors and vomiting	Operated because of perforation, released on postoperative 7th day
Sodhi *et al.* [5]	Breast cancer	38-year-old, female	Fluorouracil Epirubicin Cyclophosphamide given, later on changed with Docetaxel	7th day after Docetaxel	Acute abdomen, diarrhea and shock	Operated because of perforation, get well postoperative
Taşköylü *et al.* [6]	Breast cancer	40-year-old, female	Docetaxel Cyclophosphamide Doxorubicin	10th day of chemotherapy	Generalized abdominal pain and fever	Neutropenic enterecolitis, get well after antibiotic regimen
Oehadian *et al.* [7]	Breast cancer	61-year-old, female	Docetaxel Cyclophosphamide Doxorubicin	6th day of chemotherapy	Abdominal pain and vomiting	Operated because of perforation, released on postoperative 7th day
Rolston *et al.* [8]	Breast cancer	NA	NA	NA	NA	NA

NA = not available

method because it is considerably lower (15%) than that of US (23%) and plain radiography (48%) [7]. A wall thickness greater than 10 mm and its association with intestinal perforation are negative factors for prognosis [9]. In our case, the wall thickness in the ascending colon, and most significantly in the caecum was found to be 16 mm and peritoneal free air signs were regarded as a bowel perforation associated with NE.

In the follow-up and treatment period of NE, patients should be monitored on a daily basis, and should be fed intravenously after stopping their oral intake. In case of clinical deterioration, the patient should be assessed in terms of perforation or necrosis, and then a surgical treatment should be considered accordingly [1]. It has been reported that complications requiring surgical intervention can be encountered in 5% of patients diagnosed with NE [6]. However, most of such cases are cases with hematologic malignancies. NE-related perforation was reported in 3 patients with solid tumors treated with taxane-based chemotherapy [3, 5, 10]. According to our knowledge, our case is the 4th case in the literature in which perforation developed.

Conclusions

In conclusion, NE should be definitely considered in differential diagnosis of abdominal pain in neutropenic patients. Although perforation is rarely seen in neutropenic patients with solid tumors, it should be kept in mind and the patient should be followed-up carefully. It is noteworthy that mortality and morbidity can be reduced by means of appropriate antibiotics and a timely surgical intervention.

Informed consent

Written informed consent was obtained from the patient for the publication of this case report.

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Biceps tendon rupture diagnosed by physical examination and ultrasonography in the emergency department

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ABSTRACT

A biceps brachii rupture can occur at either superior or inferior end but most commonly involves the long head at its proximal attachment to superior glenoid labrum. We report a 48-year-old male with a proximal long-head biceps rupture because of trauma diagnosed by ultrasonography and physical examination in the emergency department. On physical examination, there was a severe pain over the anterior aspect of the shoulder, proximal part of the biceps muscle, and distally located biceps muscle mass. In ultrasonographical study, there were no tendon fibers in the right shoulder bicipital groove. The evaluation of both the physical examination and sonographic findings revealed a proximal long-head biceps rupture.

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Keywords: Biceps tendon, rupture, ultrasound

Introduction

A biceps brachii rupture can occur at either superior or inferior end but most commonly involves the long head at its proximal attachment to superior glenoid labrum [1, 2]. Trauma-related injury involves the distal part, which is rare and seen in young people [3]. Degenerative causes involve the proximal part of the tendon. We report a case with a proximal long-head biceps rupture because of trauma diagnosed by ultrasonography and physical examination in the emergency department.

Case Report

A 48-year-old male was admitted to our emergency department with sudden onset of right arm pain. He reported that he was lifting a heavy piece of machinery when he heard a sudden popping sound and now was complaining of significant swelling to his right arm.

The patient was previously healthy. He has smoking for 30 pack per year. On physical examination, there was a severe pain and tenderness over the anterior aspect of the shoulder, proximal part of the biceps muscle, and distally located biceps muscle mass (Figure 1). The right elbow active and passive range of motion was full, but there was a mild weakness with 4 of 5 powers in manual testing during elbow flexion and supination. Neurovascular examination and conventional radiographic imaging

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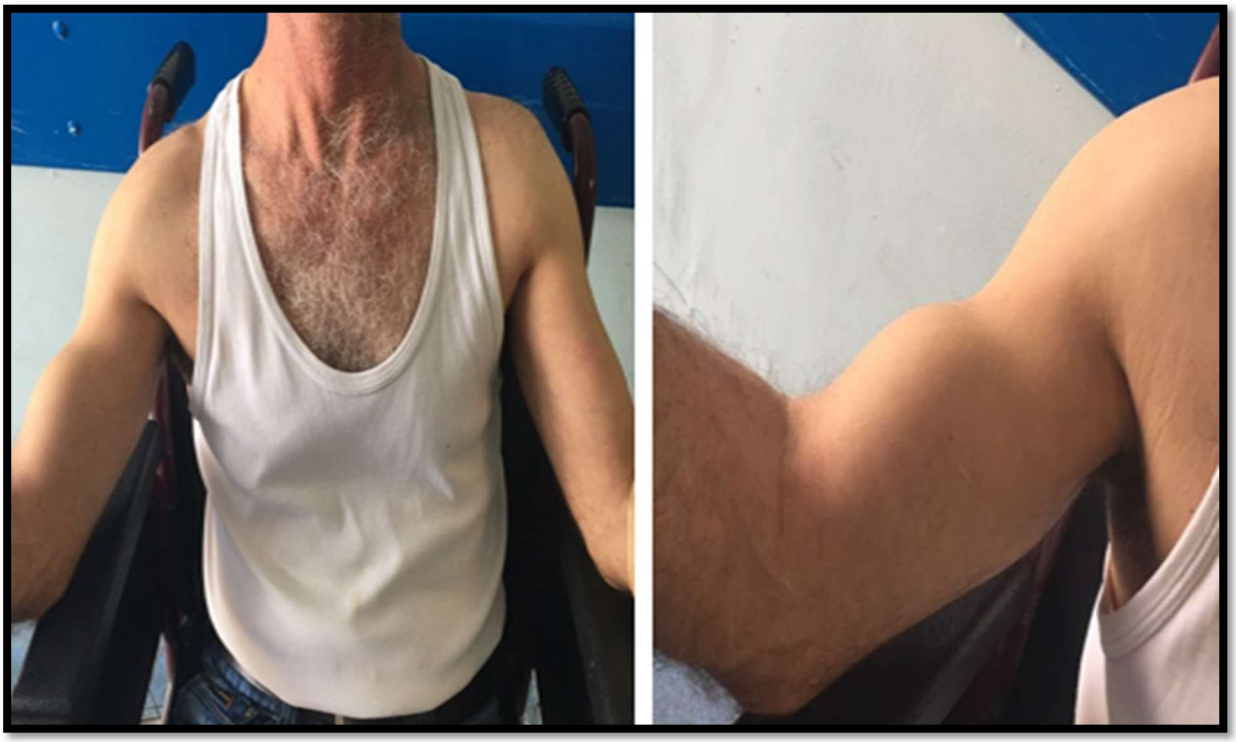

Figure 1. On physical examination, there was a severe pain and tenderness over the anterior aspect of the shoulder, proximal part of the biceps muscle, and distally located biceps muscle mass.

findings were normal. An emergency radiologist performed ultrasound (LOGIQ P5; GE Medical System, China) with a 7.5- to 12-MHz linear transducer. Ultrasound was performed while the patient was sitting, and his hand was positioned palm upward on the knee. The linear transducer was placed on the right bicipital area, and longitudinal-transverse scans were obtained. In ultrasound, there were no tendon fibers in the right shoulder bicipital groove (Figure 2). The evaluation of both the physical examination and sonographic findings revealed a proximal long-head biceps rupture. The patient was discharged from emergency department with a conservative treatment. He was placed in a sling and given pain medicine. Elective magnetic resonance imaging (MRI) was planned. He followed up in the orthopedic clinic three days later where the decision was made for surgical repair given his occupation as

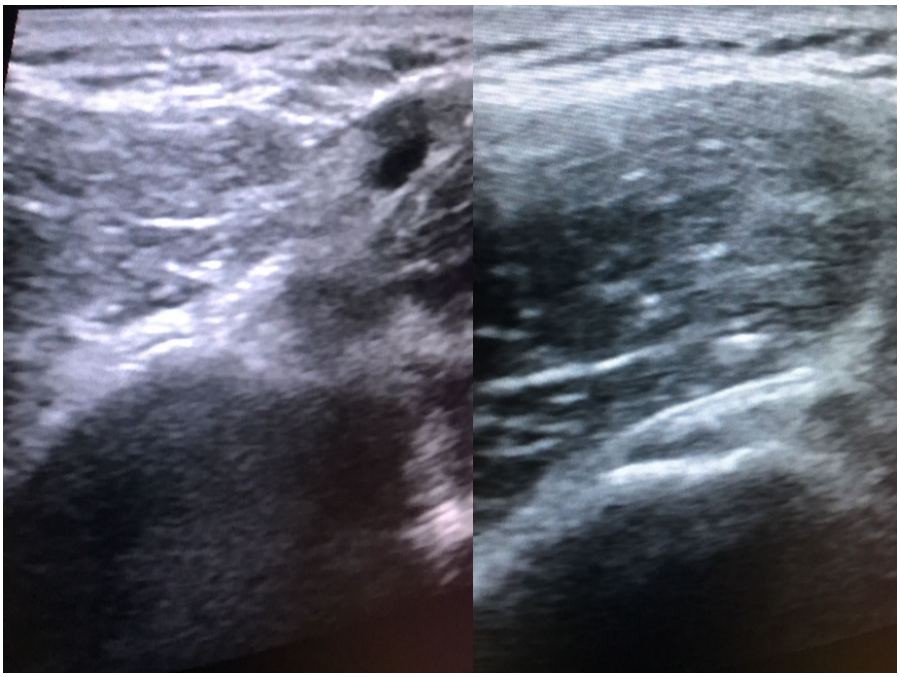

Figure 2. In ultrasound, there were no tendon fibers in the right shoulder bicipital groove

a mechanic recommendation after orthopedic evaluation.

Discussion

The biceps brachii muscle is employed in supination and flexion of the forearm. The biceps muscle has two proximal tendon additions on the scapula - the long head and the short head. The long head originates from the supraglenoid tubercle and extends over the humeral head into the intertubercular groove of the humerus. The short head arises from the coracoid process along with the coracobrachialis muscle medial to the long head tendon. The distal tendon of the biceps muscle joins to the radial tuberosity [1].

The great majority of biceps tendon ruptures occur at the proximal insertion and almost always involve the long head [1]. Most often, these ruptures occur at the bony attachment or the tendon-labral junction. Distal tendon ruptures are uncommon but can occur at the insertion on the radial tuberosity. Tendon ruptures also can happen at the short head insertion on the acromion, although this is less common.

Persons aged 40-60 years who have a history of shoulder problems that cause chronic strain on the tendon are at the highest risk for biceps tendon rupture [2]. Traumatic ruptures that occur in younger ones are usually the result of acute strain on the tendon, such as heavy weight-lifting or a traumatic fall. These often are the result of the forced extension of the elbow. Other risk factors for tendon ruptures include chronic disease states such as diabetes, chronic kidney disease, systemic lupus erythematosus, rheumatoid arthritis, chronic steroid use, fluoroquinolone use, and cigarette smoking [3].

The diagnosis of these injuries is usually made clinically [4]. Patients typically apply after an acute traumatic event where the patient experienced a sudden onset of pain, heard a "pop," and noticed bruising or swelling. Many patients with biceps tendon rupture also have a history of chronic shoulder pain due to nerve impingement.

Physical examination involves inspection of bilateral upper extremities; a biceps tendon rupture often presents as a visible or palpable mass and is referred to as a "Popeye" deformity. An examination of the affected arm should be done, and any tenderness along the biceps tendon and muscle belly should be noted.

Plain radiography is generally not diagnostic. With these graphies you can rule out bony injuries. Ultrasound is defined as a reliable indicator of biceps tendon rupture [5, 6]. MRI is often considered the "gold standard" and able to demonstrate the anatomy of the biceps tendon rupture, but is usually not applied in the emergency department.

There is debate about the final treatment of biceps tendon ruptures. Emergency care should focus on comfort measures, such as muscle relaxation by using analgesia, anti-inflammatories, and a hanger. Prompt orthopedic or sports medicine follow up is warranted for these patients and non-emergent imaging can be done for evaluation for possible surgical management. Some biceps tendon ruptures, especially those involving the long head, can be managed conservatively with pain control and physical therapy [7].

Conclusion

The diagnosis of biceps brachii tendon rupture can be easily made with physical examination and ultrasonography is a reliable imaging modality in detection of this injury.

Informed consent

Written informed consent was obtained from the patient for the publication of this case report.

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Low-grade fibromyxoid sarcoma: a rare condition with high proliferation

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ABSTRACT

Low-grade fibromyxoid sarcoma (LGFMS) is a type of high metastatic potential of the fibrosarcomas. Most of the time there is a long interval between tumor presentation and metastasis. We present 2 cases of LGFMS. The first is a 31-year-old female with a mass in anterior aspect of her left thigh, and the other is a 68-year-old female with mass in posterior of her neck. Both cases underwent operation for several times and confirmed as LGFMS histopathologically, there is no exact protocol for postoperative follow-up to detect early metastases according to the relative variety of LGFMS. So informing the patients about the long-standing metastatic potential of their disease is important.

Eur Res J 2018;4(3):238-241

Keywords: fibrosarcoma, low-grade fibromyxoid sarcoma, surgery

Introduction

No Low-grade fibromyxoid sarcoma (LGFMS) is a differentiated sub-type of fibrosarcoma. Evans first described this pathologic entity as a rare high metastatic potential soft-tissue tumor despite its benign histologic appearance in 1987 [1]. Usually pathologists, radiologists, and surgeons fall in problem for fundamental principle for tumor management due to long interval period between tumor presentation and metastasis behavior. It is still difficult to estimate LGFMS incidence because many cases are not diagnosed as LGFMS. Although LGFMS can be found in unusual places, like head, retroperitoneum,or the chest wall, these tumors usually occur in the proximal extremities and trunk [2, 3]. Subfascial location is the most common place for LGFMS occurrence, as subcutis or dermis may be affected in rare occasions [4]. LGFMS especially happen in young to middle-age adults, by the way a large member of cases have been reported in pediatric ages [3, 5, 6]. In this report, we presented 2 cases of LGFMS; a 31-year-old female with a mass in anterior aspect of her left thigh, and a 68-year-old female with a mass in posterior part of her neck.

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Case Presentation

Case 1

A 31-year-old female presented with a recurrent large tumor mass on the anterior aspect of her left thigh operated for three times before admitted to our clinic. She had been operated due to a similar tumor presentation 16 and 14 years ago at another medical center, and 6 years ago at our clinic. The mass has been growing slowly during past 6 years, but the patient did not seek for medical treatment until the tumor size disturbed her regular life. Physical examination revealed firm, multifocal, mobile masses without tenderness, redness, or warmth (Figure 1a). Laboratory evaluations and plain radiographs were unremarkable. Magnetic resonance imaging (MRI) demonstrated a contrast enhanced tumor with myxoid and fibrous pattern (Figures 1b and 1c). The tumoral masses were excised. Due to infiltration of muscular and fatty tissues, quadriceps femoris and adductor longus muscles were excised (Figures 1d and 1e). Medial and lateral parts of femoral bone periosteum were invaded by tumor and resected. After surgery the patient experienced no major complication and was discharged 5 days after the operation. The histopathological diagnosis was LGFMS (Figure 1f).

Case 2

A 68-year-old female patient presented with large recurrent tumoral masses on posterior part of her neck, radiating to her shoulders, and upward of right shoulder. During past 25 years she has been operated 3 times because of neck masses. Physical examination revealed neck stiffness and firm multifocal mobile masses especially radiated to right shoulder. There was no impairment of sensory and motor nerves. Cervical MRI demonstrated multiple sized and firm contrast enhanced masses which spread to both shoulders (Figure 2). The detected masses were excised. Periosteal infiltration was observed at spinous

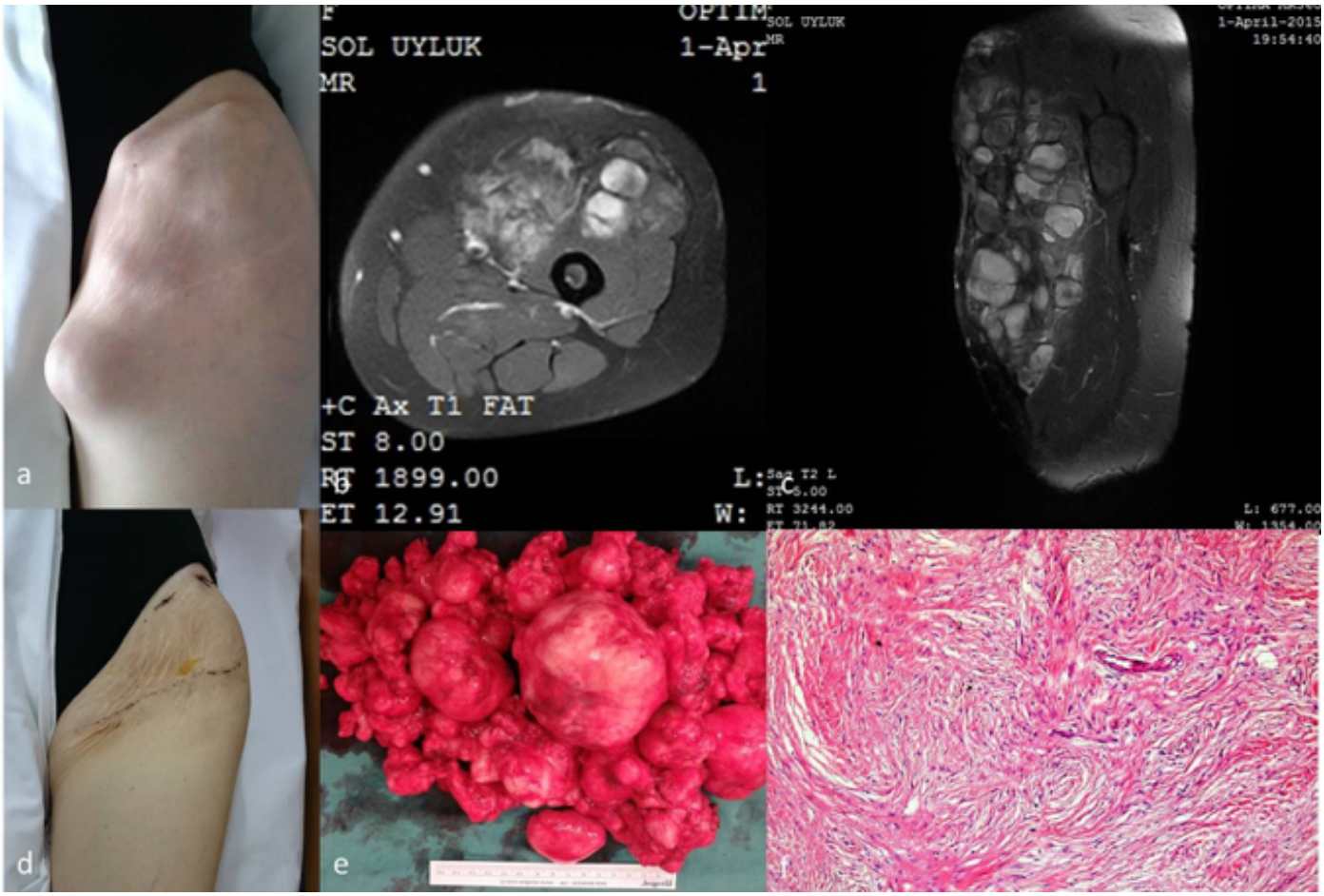

Figure 1. (a) Preoperative left leg mass; (b, c) The fibrous components were identified as hypointense area on T1- and T2-weighted MR images and slightly enhancing on T1-weighted MR images after intravenous administration. The myxoid components of the mass were recognized as hypointense on T1-weighted MR images and hyperintense on T2-weighted MR images, and enhancing on T1-weighted MR images after contrast administration; (d) Postoperative appearance of the patient's leg; (e) The excised specimen. The surface of the tumoral mass was smooth and glistering with white-gray color. There was no lenfovascular invasion or necrotic area; (f) Histopathological appearance of the mass. Immunohistochemistry study of the tumor revolves; EMA: focal positive, SMA: focal positive, MSA: negative. P53: negative, Ki 67: 3% positive.

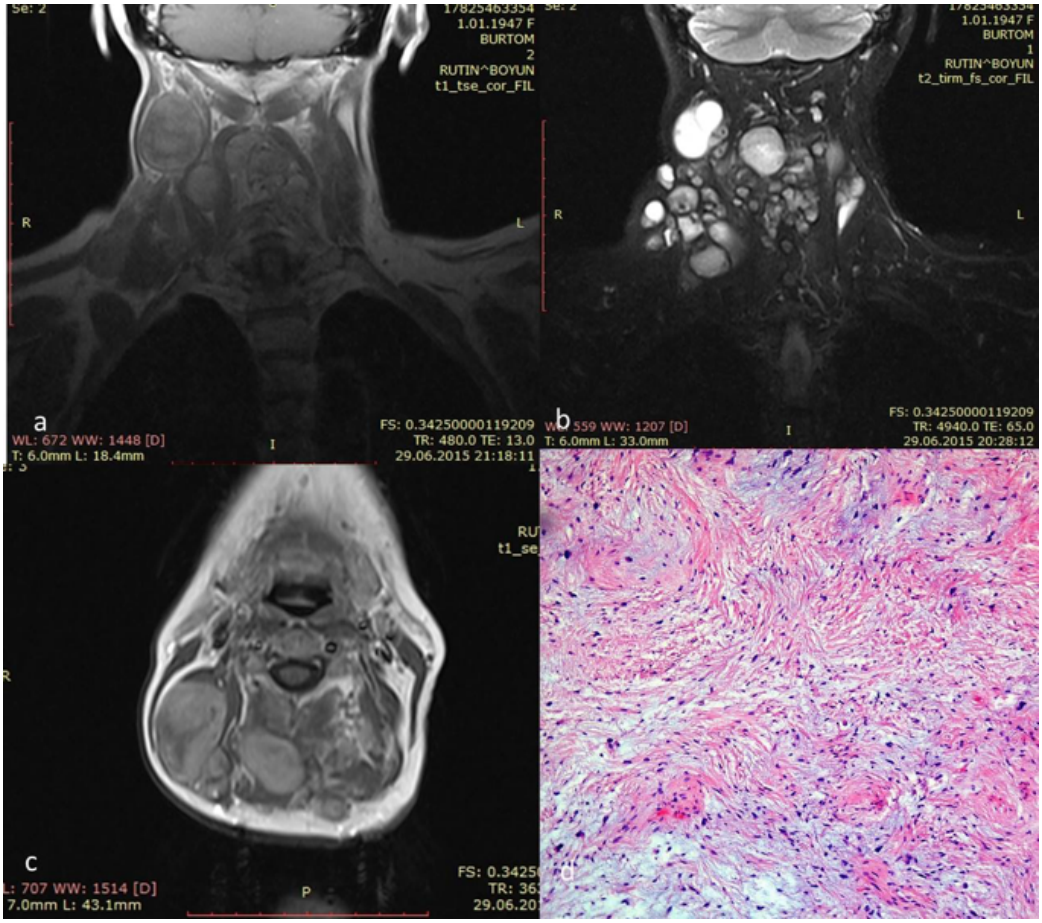

Figure 2. (a-c) C6 and C7 laminar and spinal process involvement was seen at MRI. Enhancing after contrast administration was detected as in the first case; (d) Nodular shape infiltration of hyperchromatic, pleomorphic nucleus of mesenchymal cells surrounded with fibrous stroma reported in pathological sections. Also diffused amyloid degeneration reported in tumoral section. Study of the tumor revolve; S100: strongly positive, Vimentin: strongly positive, SMA: focally positive, Desmin: strongly positive.

processes of C6 and C7 and vertebral lamina was resected together with infiltrated parts of bone. After surgery, the patient experienced no major complication and discharged 2 days after surgery. The histopathological evaluation was reported as LGFMS (Figure 2).

Discussion

TLGFMS manifestation is usually long-standing and depended on the anatomic area of the lesion. Mostly its presentation is as painless soft tissue masses with duration of over 5 years in 5% of patients [2]. Acute presentation of LGFMS is rare, and it can happen in chest wall infiltration as acute respiratory distress syndrome (ARDS) or chest pain. It may be presented with seizure when intracranial infiltration is suspected [3, 7]. In this paper we presented two cases, diagnosed at 16 years and 25 years ago.

Special MRI and CT finding for LGFMS are defined, although imaging findings are nonspecific [3, 8-10]. On CT images without contrast, the fibrous structure of these tumors interprete data density of muscular tissue, and the myxoid part was evaluated as hypodense. The fibrous structure was interpreted as hypointense on T1- and T2-weighted images, and there was a slight contrast enhancement on T1-weighted MRI images. On the other hand, the myxoid part has been found as hypointense on T1- and hyperintense on T2-weighted images, and strongly contrast enhancing on T1-weighted images. Sometimes calcification can be detected [10]. Both of our cases had contrast enhancement at radiological examination similar to literature.

LGFMS is a sub-type of fibrosarcoma, characterized by a mixture of hypercellular myxoid nodules in collagenized area with low cellularity [6]. Tumoral parts are commonly characterized by round to ovoid nuclei small cells without nucleoid and mildly eosinophilic cytoplasm. Mitosis increased at atypical region determined by hypercellularity; only in 10% of the cases nuclear hyperchromatism, and necrosis has been reported. Tumor cells are commonly determined

by absent of sparse mitotic finding, nuclear anaplasia or necrosis. It is positive for vimentin and negative for other antibodies, such as S100 protein, desmin, ceratin, epithelial membrane antigen such as CD31, and CD34 at most cases. Lesions showing proliferation of spindle cell with or without fibrous component in myxoid pattern are evaluated at differential diagnosis of LGFMS [11]. Tumors with both fibrous and myxoid pattern include fibromatosis, neurofibroma, malignant peripheral sheath tumor, perineurioma, fibrous histiocytoma, or the tumors with only predominant myxoid areas without fibrosis such as myxomas, myxoid neurofibroma, angiomyxoms, myxoid liopsarcoma, and low-grade myxofibrosarcoma have to be evaluated at differential diagnosis [10]. Also, desmoid tumors such as desmoplastic fibrosarcoma, and low-grade differentiated liposarcoma should be remembered in the differential diagnosis of LGFMS. If tumor has been removed completely, it is not difficult to diagnose LGFMS due to morphologic pattern and immune phenotypic features. In such cases, an excisional biopsy should be performed before surgical resection according to the fact that it is not commonly possible to diagnose with needle core biopsy or fine needle aspiration. If the diagnosis still remains unclear for myxoid, this kind of cytogenetic for rare cases of LGFMS can be beneficial [4].

Goodlad *et al*. [5] pointed that LGFMS were inconsistently aggressive tumor. Although all the cases were primarily diagnosed and treated as benign lesions in retrospective study, local recurrence was reported as 68%, and the death rate was reported 18% [5]. It is clear that patient selection has affected the rate of metastases and recurrence rate because most of them selected according to unexplained metastases. In another large series death rate, local recurrence, and metastasis was detected as 2%, 54%, and 6%; respectively [6]. There was no significant relation between recurrence or metastasis and the presentation of high cellularity focal area, nuclear enlargement, increased mitotic activity, and necrosis. Because of potential of late metastasis of LGFMS, as reported 45 years after primer diagnosis, these patients had to be followed for a long period of time [4]. After initial diagnosis of LGFMS the patients must be follow-up by expert oncological group. However exact interval for periodic chest imaging is unclear, as the most metastatic area is lung, several chest CT scan have to be performed during long-term follow-up of these cases.

Conclusions

The 2 cases report presented herein, enriches the literature for the best diagnosis and surgical treatment of this rare tumor. In addition, it is important to inform patients about long-time metastatic potential of the disease as there is no dedicated protocol regarding follow-up examinations for early metastatic mass diagnosis.

Informed consent

Written informed consent was obtained from the patient for the publication of this case report.

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Peripartum type A dissection: a case report

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ABSTRACT

Aortic dissection is a rare but potentially lethal complication during pregnancy in young women and usually diagnosis could be overlooked. We reported a 40-year-old postpartum female with aortic dissection which developed in peripartum period. She complained of interscapular back pain and chest pain. The patient's pain had continued after caesarean section. She admitted to our clinic six days after this intervention. Contrast-enhanced computed tomography revealed the aortic dissection. Hemiarch replacement performed successfully and the patient discharged uneventfully despite of delayed diagnosis.

Eur Res J 2018;4(3):242-244

Key Words: Peripartum aortic dissection, pregnancy complications, monitoring

Introduction

Aortic dissection during pregnancy is a rare but life-threatening complication for both mother and fetus [1]. Increased intravascular volume, heart rate, cardiac output and hemodynamic changes, occur during pregnancy. These changes are may be responsible for the increased risk for acute aortic dissections during labour and delivery or in the early postpartum period [2]. Reported cases are mostly associated with connective tissue disease (e.g. Marfan's syndrome), systemic hypertension and congenital heart disease, including coarctation and bicuspid aortic valve [3]. We reported the case of an acute type A aortic dissection occurred in a primigravid female with no noticeable risk factors just before delivery.

Case Presentation

A 40-year-old primigravid female delivered a baby with caesarean section 6 days ago, who had sudden onset of interscapular back pain and chest pain just before delivery. The patient underwent caesarean section and her chest pain had continued persistently. She had hypertension medication during pregnancy. There was no Marfanoid appearance or other appearances related with aortic dissection. Her blood pressure was 160/90 mmHg with no difference in both arms. Chest X-ray showed mediastinal enlargement but no pulmonary congestion or pleural effusion. The baseline complete blood count, serum creatinine and electrolytes were within normal limits. Contrast-enhanced computed tomography revealed type A aortic dissection starting from ascending aorta to the

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distal descending thoracic aorta (Figure 1).

After decided to emergent surgical intervention, the patient has taken to the operating room. Following right axillary artery cannulation [4-6], cardiopulmonary bypass was established. Later a sternotomy incision was made and presence of intimal tear in the supracoronary ascending aorta revealed. Under circulatory arrest with selective cerebral perfusion the arcus aorta was opened. A tear was not detected at the ostia of supra-aortic branches. We performed hemiarch replacement. The postoperative course was uneventful and the patient was discharged from the hospital on the postoperative day 7.

Discussion

According to the Stanford classification system aortic dissections evaluated as two types: type A, involving the ascending aorta regardless of the entry site location, and type B, involving the aorta distal to the origin of the left subclavian artery. Due to its high rate of mortality type A dissections requires urgent surgical approach [4]. The most common site of pregnancy-associated dissection is the proximal aorta, and aortic rupture usually occurs during the third trimester or first stage of labour [2]. There are many case reports in the literature about surgical experience at all stages of pregnancy [3].

In our patient hypertension was the known predisposing factor. It should also be stated that pregnancy is an independent risk factor for aortic dissection. Because hemodynamic changes are significantly effective in pregnant women in the second and third trimesters. These changes include increased heart rate, stroke volume, cardiac output, left ventricular wall mass, and left ventricular end-diastolic dimensions, and additionally decreased systemic vascular resistance, heart rhythm changes, and compression to the abdominal vessels by the gravid uterus [2]. Also alterations in plasma estrogen and progesterone concentrations which induced by pregnancy could be associated with aortic structural changes and lie behind the aortic dissection.

Although the clinical manifestations of acute aortic dissection are well described, the diagnosis is often overlooked in the pregnancy. In our case we have also encountered a delayed diagnosis. Acute aortic dissection has an estimated mortality rate of 1 to 2% per hour during the first 24 to 48 hours of onset if remains untreated [7]. Rajagopalan *et al*. [8]reported a maternal mortality rate of 21% for type A and 24% for type B aortic dissections in 75 pregnant women. The fetal mortality rate was 10% for type A and 35%

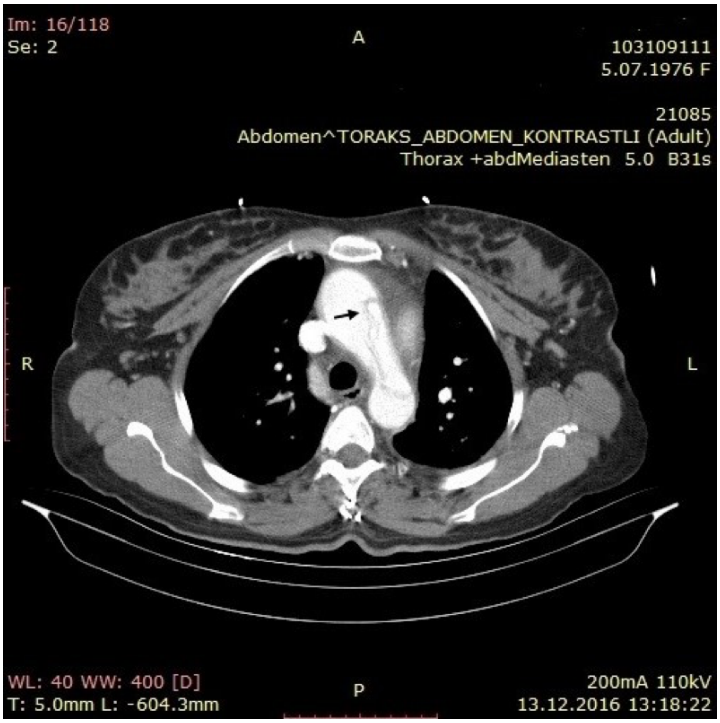

Figure 1. Intimal flap imaging (arrow) at the transverse arch

for type B aortic dissections [8]. The patients which has predisposing factor such as hypertension due to preeclampsia, congenital heart disease, coarctation of the aorta or connective tissue disorders as Marfan syndrome, should be closely monitored. For our patient, we performed hemiarch replacement and in despite of delayed intervention outcomes were sufficient. Late presentation and delayed diagnosis may cause death in these patients. If any symptom begins suddenly such as severe, sharp pain in the chest and interscapulary area aortic dissection must be considered.

Conclusions

A 40-year-old female with type A acute aortic dissection which developed just before delivery, treated successfully by hemiarch replacement six days after delivery. This case has some highlights for gynaecologist and cardiovascular surgeons. After onset of acute complaints caesarean section has been performed but not suspicious presence of aortic dissection. She could have lost her life in this six days.

Informed consent

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Re-expansion pulmonary edema after pleurocan catheterization: a case report

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ABSTRACT

Re-expansion pulmonary edema (RPE) is a rare but potentially hazardous complication following evacuation of the pleural region. Symptomatic RPE occurs in less than 1% of patients after pleural drainage. Early diagnosis and treatment determines the progression of the disease and it is life-saving. The present case describes a 68-year-old man who developed RPE with the ipsilateral collapsed lung 6 hours after pleural drainage of a non-malignant effusion. He was intubated and 6 hours after aggressive treatment with mechanical ventilation support oxygenation was improved and the patient's blood gas analysis recovered. Over the course of his 12-day hospitalization, he was extubated and oxygen support was slowly weaned down. Mortality rate of RPE in severe cases is approximately 20%, therefore preventive interventions gain importance. In spite of the rare incidence of RPE, being aware of this potential condition can allow for early and proper management.

Eur Res J 2018;4(3):245-247

Keywords: Re-expansion pulmonary edema, pleural catheter, intensive care

Introduction

Re-expansion pulmonary edema (RPE) is a rare but potentially hazardous complication which may occur in every kind of chronically collapsed lung, following evacuation of the air or fluid from the pleural region. Most cases are clinically mild and detected incidentally on radiography so the true incidence is still skeptical (0.9-20%), but symptomatic RPE occurs in less than 1% of patients after pleural drainage [1].

Mostly, RPE is limited to the ipsilateral lung after relief of collapse and the main signs are tachypnea, tachycardia, and crackles on the affected side of the lung. Generally, a chest radiograph is sufficient for diagnosis, but the suspect of the clinician is essential. The radiographic diagnosis includes the presence of opacities in the previously collapsed lung, following thoracentesis. Because of the clinical and radiological diversity of RPE, cardiogenic pulmonary edema, pulmonary infections and pneumonitis should be kept in mind in the differential diagnosis. Early diagnosis and treatment determines the progression of the disease and it is life-saving [2]. The present case describes a 68-year-old man who developed RPE with the ipsilateral collapsed lung 6 hours after pleural drainage of a non-malignant effusion.

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Case Presentation

A 68-year-old man with cholangiocellular carcinoma diagnosis who had been operated in our hospital followed up for respiratory distress. He had progressive dyspnea over the course of several days. The initial radiographic assessment revealed massive pleural effusion in the right hemithorax (Figure 1). At first, an 8.3-French pig tail catheter drainage for the pleural effusion was performed and the cytology findings of the effusion were negative for malignancy. Then pleurocan catheter was implanted under local anesthesia and the initial amount of drainage was serosanguinous fluid of 1000 ml in 1 hour period. The patient tolerated the procedure well and his symptoms improved. However, 6 hours after the pleural drainage the clinical manifestation of tachypnea, dyspnea and tachycardia was observed, and his oxygen saturation dropped to 80% on room air. A chest radiograph taken at that time showed bilateral opacities resembling ARDS, suggesting RPE in the whole lung field (Figure 2).

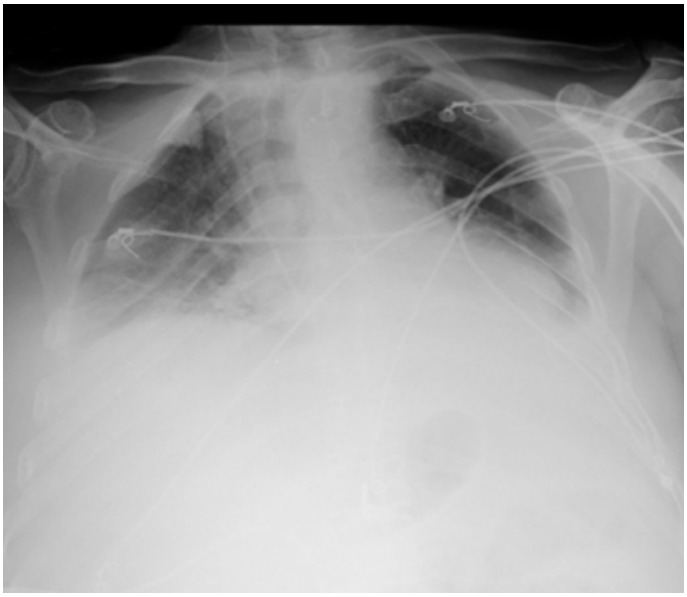

Figure 1. Massive pleural effusion in the right hemithorax.

As a conservative treatment fluid intake was restricted, diuretic and supportive oxygen therapy started. Cardiogenic edema was completely excluded by the mean of transthoracic echocardiography examination. More aggressive diuresis was avoided to protect from hypotension and cardiovascular collapsed in the setting of RPE.

The patient clinic situation worsened with extensive crackles in the bilateral lung auscultation. Blood gas analysis of the patient revealed pH: 7.13,

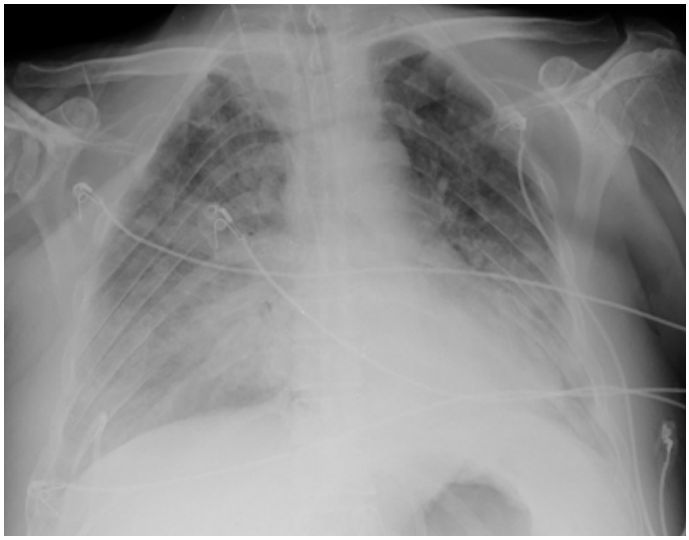

Figure 2. A chest radiograph taken at that time showed bilateral opacities resembling ARDS, suggesting re-expansion pulmonary edema in the whole lung field.

PaCO2: 56.4 mmHg, PaO2: 36.2 mmHg, HCO3: 18 mEq / L, base deficit: (-7) and orotracheal intubation became inevitable. He was placed on pressure-regulated pressure control with FiO2: 80%, PEEP: 8 cmH2O, frequency: 15/min and pressure support: 18 cmH2O. Six hours after this aggressive treatment with mechanical ventilation support oxygenation was improved and the patient's blood gas analysis recovered (pH: 7.42, pCO2: 28.4 mmHg, pO2: 104 mmHg). Ventilator settings were weaned to a PEEP of 5 and FiO2 of 40%. It was observed that the chest x-ray findings also recovered within 24 hours and the RPE resolved (Figure 3). Over the course of his 12-day hospitalization, he was extubated and oxygen was slowly weaned down.

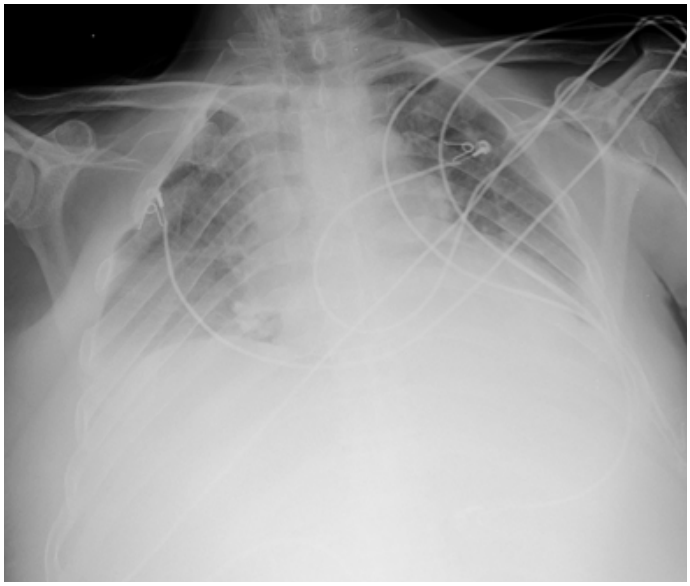

Figure 3. Chest x-ray findings also recovered within 24 hours and the re-expansion pulmonary edema resolved.

Discussion

Mostly, RPE is limited to the ipsilateral collapsed lung after relief of collapse and occurs within 24 hours. The clinical appearance of RPE can range from asymptomatic radiographic findings to fatal hypoxia. Although there is no consensus for exact mechanism for RPE, major risk factors that have been proposed are rapid re-expansion, drainage with the use of negative intrapleural pressure, and chronicity of lung collapse [3]. Increased permeability of the pulmonary capillaries as a result of inflammation is mainly accused for pathophysiology [2]. In some studies, it was shown that ventilation and reperfusion of a previously collapsed lung may lead to an inflammatory response increasing capillary permeability and results in RPE [4].

Pressure-induced mechanical disruption of the alveolar capillaries, and altered lymphatic clearance are the other accused factors for RPE development. We speculate that in our case, those factors and surgical stress during abdominal operation may have induced a subclinical pulmonary inflammation, that may have ensured a second impact mechanism for the development of the RPE. Even though these factors might partake to the formation of RPE, maybe none of them is indispensable. This might explain the difficulty of prediction in the occurrence of RPE [5].

Early recognition is essential in ensuring successful treatment of RPE and the anchor of treatment remains generally conservative and supportive like sufficient oxygen supplementation, while in severe cases more intensive treatments such as mechanical ventilation is required [3]. In patients requiring orotracheal intubation and mechanical ventilation support, as in our case, positive end expiratory pressure (PEEP) usage improves symptoms after 24-48 h. There is often underestimation of the morbidity and mortality associated with pleural interventions . Mortality rate of RPE in severe cases is approximately 20%, therefore preventive interventions, including the use of low negative pressure for suction and limiting drainage to about 1 to 1.5 L of pleural fluid gain importance, though the data is limited. [6, 7].

Conclusions

In spite of the rare incidence of re-expansion pulmonary edema, being aware of this potential condition can allow for early and proper management.

Informed consent

Written informed consent was obtained from the patient for the publication of this case report.

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Authors' contributions

All authors participated in the design of the case report and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

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Celiacomesenteric trunk: A rare case

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ABSTRACT

We present a case of celiacomesenteric trunk that was incidentally detected on routine multi-detector row computed tomography angiography of lower extremities. A 59-year-old patient had intermittent claudication. The celiacomesenteric trunk is a rare vascular variation that is important to be detected before surgical and interventional procedures. Multi-detector row computed tomography angiography is excellent on showing vascular anatomy, pathology and variations.

Eur Res J 2018;4(3):248-250

Keywords: Celiacomesenteric trunk, celiac trunk, superior mesenteric artery, mesenteric vascular variation, multi-detector computed tomography angiography

Introduction

The celiac trunk and superior mesenteric artery are the most important visceral branches of abdominal aorta, supplying nearly total blood flow for gastrointestinal tract. The celiac trunk generally originates from ventral part of abdominal aorta at the level of 12th thoracic vertebrae and branches off the left gastric, common hepatic and splenic arteries. The superior mesenteric artery generally arises at the level of first lumbar vertebrae, about 1 centimeter below the origin of the celiac trunk [1].

The celiacomesenteric trunk is a rare (1-2%) vascular variation which has clinical importance especially before surgical or interventional radiological procedures. The superior mesenteric artery and the celiac trunk arises from a single trunk [2].

Multi-detector computed tomography angiography (MDCTA) has an excellent performance and more comfortable for the patient, to show vascular anatomy, pathology and variations [3].

Case Presentation

During the MDCTA scan of a 59-year-old man complaining intermitting claudication (an aching, crampy, tired or burning pain in the legs - typically occurs with walking and goes away with rest - due to poor circulation of blood in the arteries of the legs), a stunning variation was detected. The celiac trunk and superior mesenteric artery were seen to originate from a common trunk from ventral part of abdominal aorta

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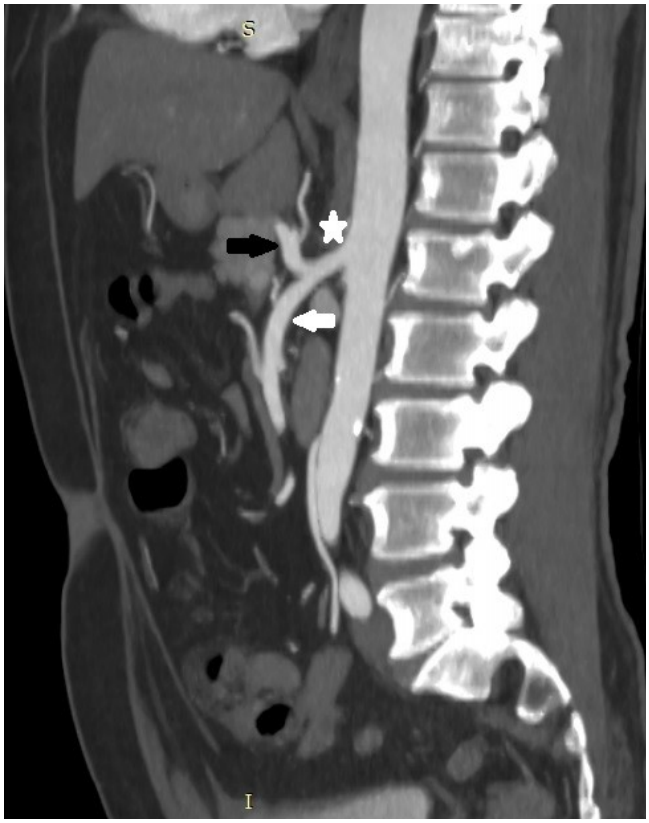

Figure 1. Sagittal maximum intensity projection (MIP) image of the case; origin of celiacomesenteric trunk (star), the celiac trunk (black arrow) and the superior mesenteric artery (white arrow).

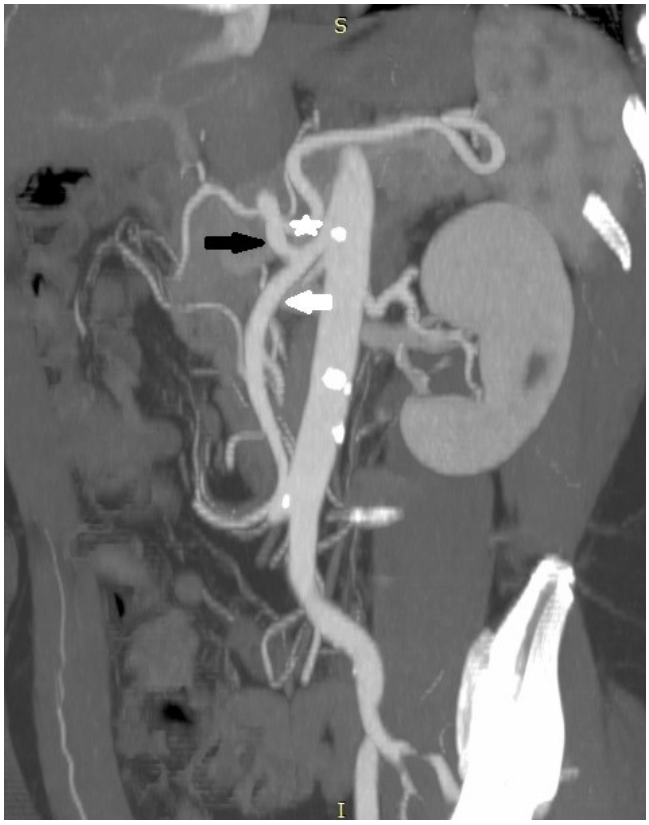

Figure 2. Coronal maximum intensity projection (MIP) image of the case; origin of celiacomesenteric trunk from abdominal aorta (star), the celiac trunk (black arrow) and the superior mesenteric artery (white arrow).

(Figures 1, 2, and 3). The celiacomesenteric trunk was to be length of 14 mm and 12 mm in diameter. The celiac trunk was 9 mm, and the superior mesenteric artery was 8.5 mm in diameter.

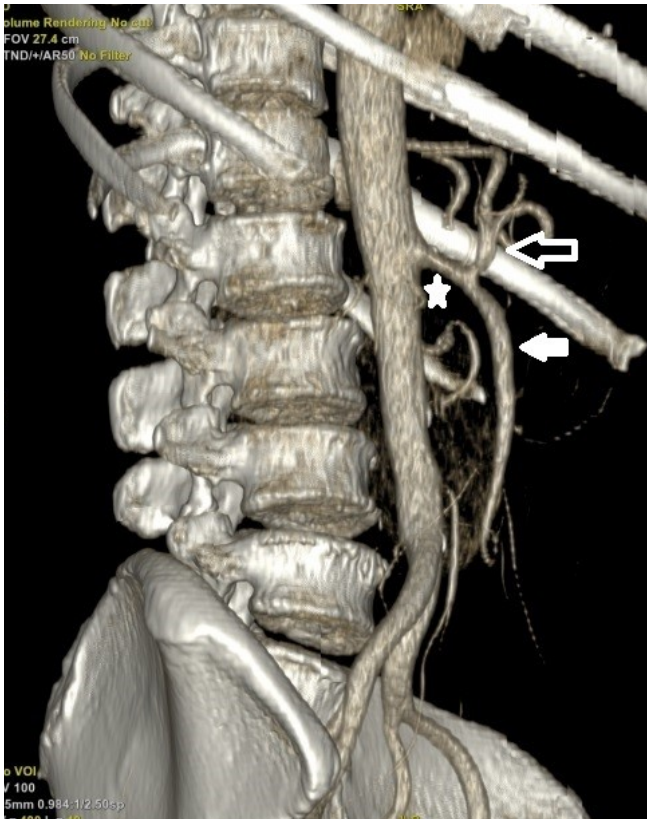

Figure 3. Volume rendering image of celiacomesenteric trunk (star), the celiac trunk (empty arrow) and the superior mesenteric artery (white arrow).

There was no variation on the celiac trunk and superior mesenteric artery branching; left gastric, splenic and common hepatic arteries were originating from the celiac trunk, inferior pancreaticoduodenal, jejunal, ileal, middle colic, right colic, ileocolic arteries originated from the superior mesenteric artery.

Discussion

In general population, the celiac trunk arises from the abdominal aorta and branches into left gastric, splenic and common hepatic arteries. The superior mesenteric artery arises from the abdominal aorta, too, and branches into inferior pancreaticoduodenal, jejunal, ileal, right colic, middle colic and ileocolic arteries.

The celiacomesenteric trunk is a rare variation which is presenting that the celiac trunk and superior mesenteric artery arises from a common trunk. A review showed the incidence of the celiacomesenteric

trunk is in the rate of 2% [4]. Matusz *et al.* [5] reported that 0.68% of cases. Tandler [6] provided an embryological theory for the celiac trunk and superior mesenteric artery variations. In embryologic life, retention of the ventral longitudinal anastomosis and disappearance of the first or fourth vascular root, causes a celiacomesenteric trunk [6].

The celiacomesenteric trunk is usually discovered incidentally during radiologic imaging or cadaveric dissection by anatomists. It is substantial to be aware of this rare variation. Because if it is thrombosed or injured, the blood supply of abdominal viscera is dramatically blocked. On the other hand it is very important to report if the celiacomesenteric trunk exists before surgical or interventional radiologic procedures.

Conclusions

In conclusion, the celiacomesenteric trunk is an important vascular variation that is usually asypmtopmatic. But it must be kept in mind for the patients that will undergo surgical or radiologic aortic procedures.

Informed consent

Written informed consent was obtained from the patient for the publication of this case report.

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Quadriceps tendon rupture associated with anabolic steroids and growth hormone: a case report

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ABSTRACT

Androgenic and human growth hormone derivatives have to potential to increase athletic performance despite increased risk of serious adverse effects. The risk of tendon rupture is very high in the anabolic androgenic steroid users. A 51-year-old male admitted to the emergency department with left knee pain following sport training. He had a history combination of androgenic hormones and insulin growth factor -1 use. Magnetic resonance imaging showed swelling, heterogeneity and partial discontinuity of the quadriceps tendon. Use of performance enhancing drugs has become a serious public health problem. Due to increase of abuse today it is possible to encounter more side effects in the future and has to be considered as a growing public health problem.

Eur Res J 2018;4(3):251-253

Keywords: quadriceps tendon rupture, androgenic hormone, growth hormone

Introduction

Quadriceps tendon rupture is a rare condition in the absence of systemic disease. Some athletes use hormonal drugs to improve their performance, personal appearance and to increase their muscle mass [1]. Especially, the use of androgenic and derivative of biosynthetic human growth hormone has become serious global health problem despite controls and injuries related with them. These drugs showed increased risk of tendon ruptures who are relatively common in bodybuilders [2]. We report partial rupture of quadriceps tendon rupture in a bodybuilder who had taken anabolic steroid and growth hormone for years.

Case Presentation

Our patient is 51-year-old, healthy, white male, previously professional national class bodybuilders. He ranked first place in his weight class in Turkey national body-building championship, two years ago. He was admitted to our emergency department with left knee pain following sport training. He experienced sudden severe pain in his right knee after attempting front squat 150 kg of weight. He reported a history combination of androgenic (nandrolone) and insulin growth factor-1 use that he had stopped before 6 months. He had also been previously insulin resistance, cardiac hypertrophy and left biceps tendon rupture (20 years ago).

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On examination he was unable to walk and straight leg raise. He has also hematoma and swelling in left knee. Magnetic resonance imaging (MRI) of the left knee joint was performed using a 3T unit. Sagittal and axial T1-weighted and proton- density weighted images with fat saturation were obtained. MRI showed swelling, heterogeneity and partial discontinuity of the quadriceps tendon (Figure 1). Partial tear of the quadriceps tendon was diagnosed. Immobilization with full extension was recommended.

Discussion

Use of performance enhancing drugs has become a serious public health problem. The overall lifetime prevalence for use of the androgenic hormones rate was 6.4 percent in men, 1.6 percent in women [3]. Performance enhancing drugs are anabolic androgenic steroids, androstenedione, human growth hormone, erythropoietin, diuretics, creatine and stimulants. Frequently, the anabolic androgenic steroids that body-builders use are synthetic modifications of testosterone. The most commonly used androgens are testosterone, trenbolone and boldenone [4]. They assist athletes by facilitating efforts to gain strength and muscle mass for increased muscular endurance and power. They promote an increased nitrogen concentration in muscle; which promote anabolic state. Usually they can be taken as injections and pills. It is estimated that 1 million men have experienced these drugs [5].

There are many adverse effect of anabolic steroids and some can be serious and mortal. Case reports describe sudden death in young athletes who were taking androgens [6]. The most important and common side effects of anabolic steroids are gynecomastia, infertility, impotence in men [7] and a deeper voice, increased body hair, cliteromegaly, infrequent or absent menstrual periods in women [8]. Both men and women also have increased risk of severe acne, liver abnormalities and tumors, high blood pressure, heart circulatory problems [9], increased aggressiveness [10], psychiatric disorders [11], injection disease such as HIV or hepatitis [12] and decrease serum high density lipoprotein (HDL) and increase low density lipoprotein (LDL) [13].

Human growth hormone is a hormone that has an anabolic effect. Athletes take it to improve muscle mass and performance like testosterone derivatives. It is only administered by injection. Growth hormones like androgenic hormones, has been used, approximately 5 percent of United States high school students report using these [14]. The most common adverse effect related to growth hormone are joint pain, myopathy, carpal tunnel syndrome, impaired glucose regulation, sodium retention, cardiomegaly, high cholesterol and high blood pressure [15, 16]. Usually the degree and the severity of these side

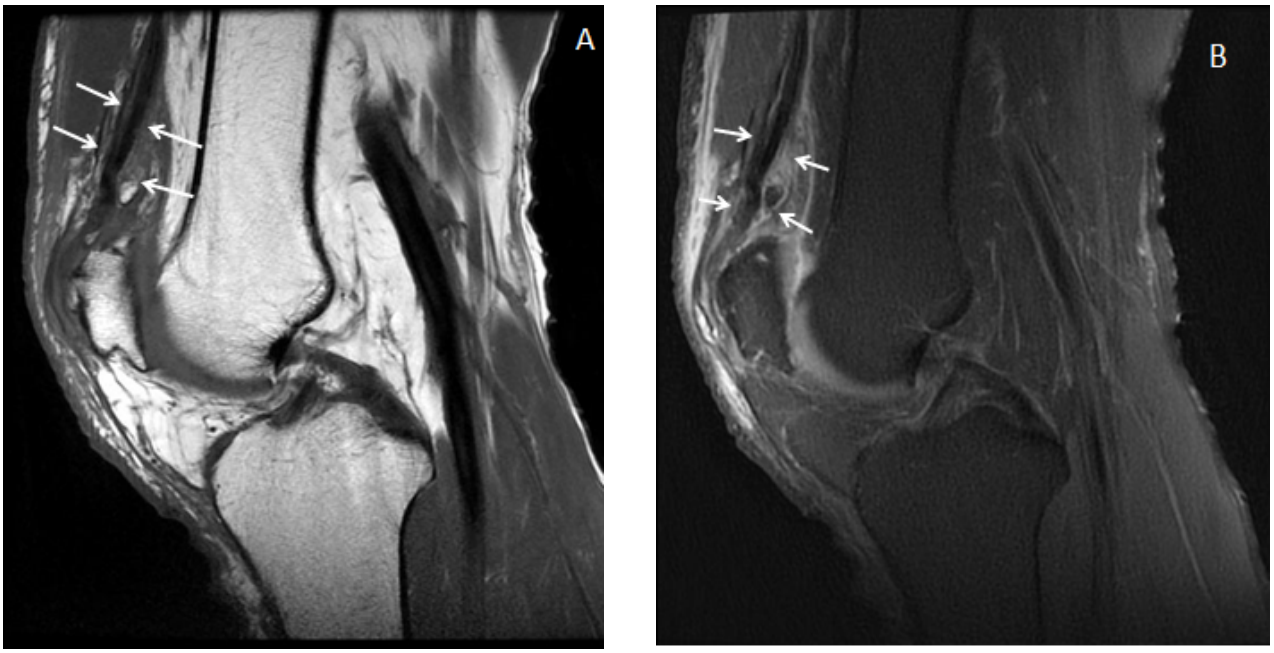

Figure 1. Sagittal T1 weighted image (**A**) and sagittal proton-density fat suppressed image (**B**) reveal enlarged and edematous quadriceps tendon and a fluid collection within the tendon (arrows), suggestive of partial rupture of the quadriceps tendon.

effects are often decrease with the cessation of the drug use. But it should not be forgotten that individuals will respond differently depending on each person's unique body physiology.

Some of the side effects that are associated with steroid use are tendinitis and tendon ruptures [17, 18]. There are several case reports regarding tendon ruptures associated to the anabolic steroids but very few of them are in the quadriceps tendon. The risk of tendon rupture is 9.0 times greater in the anabolic androgenic steroid users. The incidence of lover extremity tendon ruptures is much less than that for upper extremity ruptures. Simultaneous quadriceps rupture occurs commonly between ages 27 and 54. Quadriceps tendon rupture is usually associated with some chronic diseases like renal failure, diabetes, and gout. In addition, case of performance enhanced drug use have also been reported. The most common cause of quadriceps tendon rupture appears to be sudden contraction of the quadriceps with knees.

Conclusions

Performance-enhanced drug abuse has a substantial public health problem. The use of androgens, growth hormone and other drugs have an increased adverse effect. Although these drugs are prohibited, their use are very common. Due to increase of abuse today it is possible to encounter more side effects in the future and has to be considered as a growing public health problem.

Informed consent

Written informed consent was obtained from the patient for the publication of this case report.

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Refractory status epilepticus responding to lidocaine: A case report

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ABSTRACT

Status epilepticus is a life-threatening condition, which is associated with a high mortality and morbidity when left untreated. It is defined as a continuous seizure lasting more than 30 min or successive seizures with no recovery between any of them. Mortality of status epilepticus depends on the duration and type of seizure, concomitant diseases and age of the patient. Management of status epilepticus includes ensuring adequate airway, stabilization of circulation and use of antiepileptic drugs. Benzodiazepines, phenobarbital, phenytoin, fosphenytoin, general anesthesia and lidocaine are used for the treatment of status epilepticus. Here, we discuss a patient with refractory status epilepticus who achieved a very good response and full recovery only with lidocaine infusion among all forms of therapy given.

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Keywords: status epilepticus, lidocaine, antiepileptic drugs

Introduction

Two or more successive epileptic seizures that fail to respond to antiepileptic drug therapy should be considered drug-resistant and a distinct treatment strategy should be followed in such patients. This presentation of epilepsy usually involves respiratory and cardiovascular problems and associated systemic complications. Status epilepticus has a high mortality when left untreated. Status epilepticus mortality is higher in the elderly and lower in childhood. In many cases, systemic and metabolic derangements related to status epilepticus cause neuronal damage and cellular impairment. Refractory status epilepticus is a form of epilepsy that fails to respond to therapy and involves continued seizure activity as demonstrated by clinical and electroencephalographic findings. Several antiepileptic agents are used for its treatment at predefined dose ranges and protocols [1, 2]. In this paper, we will discuss a case of refractory status epilepticus in a case with no previously diagnosed epilepsy who reported having ten generalized tonic-clonic seizures successively on the same day at her first presentation and responded only to lidocaine despite administration of full range of antiepileptic drug therapies.

Case Presentation

A 16-year-old female, right-handed student was

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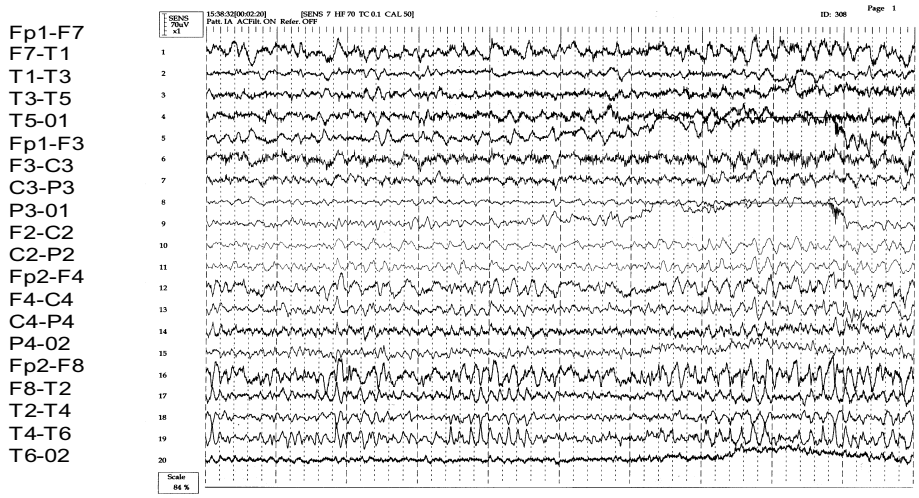

Figure 1. Ictal activity originating from the right frontotemporal area.

brought by her family to our emergency room after experiencing ten generalized tonic-clonic seizures successively on the same day with loss of consciousness. She had no history of seizures and suffered a complex partial seizure that developed a week ago involving gazing at a fixed point, not responding when questions were directed and pulling on her clothes obsessively 2-3 times a day. Prior to admission to emergency room, she had a total of six generalized tonic-clonic seizures in the last 3 days. Neither personal nor family history indicated remarkable risk factors or characteristics. On neurological examination, she was unconscious, non-responsive to verbal and painful stimuli. Brainstem reflexes were present with bilaterally extensor plantar skin reflex and no facial asymmetry.

During her emergency room stay, she developed sudden and rapid onset of eye deviation, head deviation to the right with persistent generalized tonic-clonic seizures. An emergency computed tomography scan of the brain did not show acute pathology. While her vital findings were stabilizing, diazepam was administered intermittently at a dose of 30 mg/day by intravenous route. The patient was transferred to the neurology intensive care unit (ICU) and phenytoin infusion was given at a dose of 30 mg/kg. During that period, she was unconscious with persistent complex partial and generalized tonic-clonic seizures, eye deviation, and hand automatism; therefore, she was intubated and midazolam infusion (0.4 mg/kg/h) was initiated. At 12 hours after her admission, her clinical seizure activity decreased, and vital findings were stabilized and a lumbar puncture was performed. Cerebrospinal fluid examination and cranial magnetic resonance imaging showed normal findings.

An electroencephalogram showed continuous seizure activity originating from the right frontotemporal area spreading to the left and right hemispheres (Figures 1, 2a and 2b). Thus, phenytoin and midazolam infusion were maintained on the

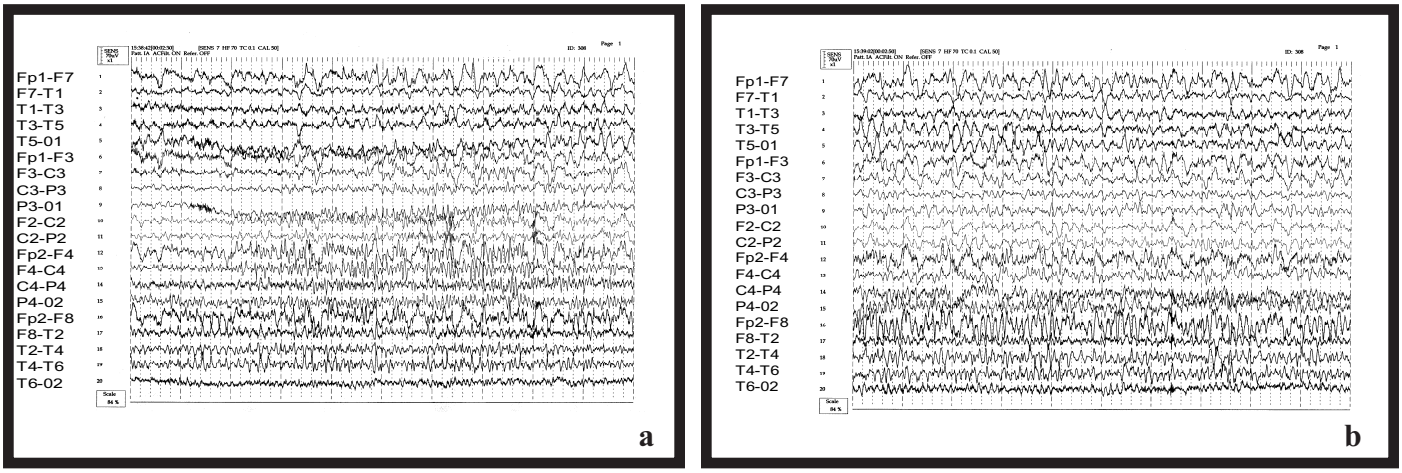

Figure 2. Spreading of the ictal activity originating from the right frontotemporal area to the left hemisphere (a). Spreading of the ictal activity originating from the right frontotemporal area to the right hemisphere (b).

second day of her admission. A follow-up electroencephalogram on day 3 showed persistent seizure activity; therefore, carbamazepine was added to the treatment, thiopental infusion (5 mg/kg/h) was initiated and midazolam infusion discontinued by tapering. Since clinical and electrophysiological seizures were resolved at that time, attempts were made to reduce thiopental infusions on two occasions, but seizure activity recurred first electrophysiologically and then clinically. Thus, lidocaine infusion (3 mg/kg/h) was started on day 8 and thiopental infusion was tapered and then stopped altogether. On the third day of lidocaine infusion, full seizure control was achieved both electrophysiologically and clinically. She gradually gained consciousness and was maintained on phenytoin 3×125 mg and carbamazepine 1200 mg/day thereafter.

During her hospitalization, she was put on and weaned from mechanical ventilation four times and in addition to her manifestations, pneumonia, gastrointestinal bleeding, elevation of liver function tests and thrombocytopenia developed. Topiramate was added to her treatment with gradual discontinuation of phenytoin.

During follow-up, the patient became fully conscious and alert and was transferred from the ICU to the neurology ward on day 15. The patient is currently on maintenance therapy with topiramate 200 mg/day and carbamazepine 1200 mg/day with no seizures for 2.5 years.

Discussion

Epileptic patients may enter the phase of status epilepticus at some point during the course of their disease with an incidence of 1.3-1.6%. The most common cause of status epilepticus is the withdrawal of the antiepileptic drug. Status epilepticus is associated with a high rate of mortality which ranges from 8 to 32%. This rate may vary depending on the underlying etiology and concomitant conditions. Permanent neurological sequelae can occur in patients with prolonged status epilepticus. Cerebral damage related to status epilepticus may also develop entirely independently of systemic complications. This kind of independent neuronal damage is believed to develop as a result of increased metabolic demand through calcium-dependent excitotoxicity, glial metabotropic glutamate receptors and excessive neuronal activity [1-3]. Recent arguments suggest that certain surgical epilepsy interventions (such as focal resection or multiple subpial transection) may be needed for the treatment of refractory status epilepticus in carefully selected cases who are nonresponsive to repeated courses of medical therapy. Prognosis is often poor in refractory status epilepticus but the observation that many patients achieved full neurological recovery over the years suggests that it might be wrong to stop treatment prematurely [4].

A crucial step in the management of status epilepticus is "suspecting, scanning and sorting" which involves suspecting the disease in an early stage, performing neuroradiological imaging studies needed for the diagnosis and obtaining an electroencephalogram. Treatment should begin with stabilization of the vital findings, followed by correction of any electrolyte imbalance and resolution of fever. Since the risk of secondary infection is high, treatment with an appropriate antibiotic should be initiated and a lumbar puncture performed for differential diagnosis when deemed necessary. For specific treatment, antiepileptic therapies should be used by careful patient monitoring in an intensive care setting since these medications are toxic and may lead to respiratory depression. Benzodiazepines are first-line therapy. Diazepam, lorazepam and midazolam are the most commonly used agents. They have a rapid onset of action and penetrate readily into the cerebral tissue due to high fat solubility. Their major side effects include respiratory depression. Broad-spectrum antiepileptic drugs such as phenytoin and fosphenytoin are used in the second-line treatment as loading and maintenance doses in status epilepticus. Phenobarbital may be given to patients who do not benefit from benzodiazepines or phenytoin with vigilance for respiratory depression [5].

Parenteral valproate has been used since 1997. It can be used for rapid seizure control and in patients who cannot be orally fed. Recent studies comparing the efficacy of parenteral phenytoin and parenteral valproate in the treatment of refractory status epilepticus showed no statistically significant difference. It was suggested that valproate may be a good alternative to phenytoin particularly in patients with cardiopulmonary disease [6].

Additionally, intravenous levetiracetam may be used safely for the treatment of benzodiazepine-refractory status epilepticus in selected cases, especially in patients with liver failure, elevated liver enzymes or cardiac arrhythmias [7]. For treatment of

status epilepticus refractory to phenytoin and benzodiazepines, lidocaine, rectal valproate, magnesium sulfate, rectal benzodiazepine and rectal chloral hydrate may be used [8]. General anesthesia may be performed in case of failure to achieve response to these therapies.

Lidocaine was first used in 1955 by Bernhard, Boem and Hojebag. Since then, it has been used in patients non-responsive to diazepam, phenytoin, phenobarbital or general anesthetic agents. Lidocaine is a sodium channel blocker. There are both individual case reports and case series published on refractory status epilepticus responding to intravenous lidocaine. Since lidocaine does not cause respiratory depression, it was suggested that it might be good therapeutic option particularly in patients with a chronic lung disease or no response to diazepam. Generally, it is recommended that administration of lidocaine should be continued until epileptic seizure resolves. Some studies have reported both lack of efficacy and harmful effects of lidocaine in many patients. Therefore, administered lidocaine dose should not exceed 2-3 mg/kg of body weight [9].

Generalized status epilepticus has an average mortality rate of 20% (range, 3-35%). Anorexia is the most common cause of mortality (60%). The currently presented case is particularly interesting since the patient responded very well only to lidocaine despite administration of several lines of therapy and no occurrence of neurological deficits although she was put to and weaned from mechanical ventilation many times and treated in the ICU with a clinical picture of status epilepticus for two weeks.

Conclusions

Refractory status epilepticus is a difficult-to-treat condition which demands patience and a step-wise management approach. Throughout the course of treatment, seizures occurring in the patient should be clearly identified both clinically and by electroencephalogram and the choice of drug should be based on the age, metabolic condition of the patient and underlying cause of the disease.

Informed consent

Written informed consent was obtained from the patient and patient's family for the publication of this case report.

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Authors contribution

Author were involved in the study conception and design. Author provided input to the discussion, interpreted the findings, assisted in writing of the draft manuscript, reviewed the manuscript for intellectual content, and read and approved the final manuscript.

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Charcot neuroarthropathy of the hand in a diabetic patient after upper extremity trauma

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ABSTRACT

Charcot neuroarthropathy is a progressive degenerative arthritis which affects nearly every joint of the body associated with an underlying central or peripheral neurological disorder and can cause severe disability. The joints most frequently involved are lower limbs especially foot, shoulder and elbow. However, Charcot neuroarthropathy of the hand is quite rare. Herein, we present a 50-year-old diabetic female patient with CNA of the right hand after upper extremity trauma. Major or minor traumas in diabetic patients can increase the risk of CNA on upper extremity as a complication of diabetes mellitus.

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Keywords: Charcot neuroarthropathy, diabetes mellitus, trauma

Introduction

Charcot neuroarthropathy (CNA) firstly recognized in 1868 by Jean Marie Charcot, still remains a clinical problem. There is a progressive disorganization of architecture in the intensive joint, leading to painless joint swellings with radiological evidence of pronounced bone destruction as well as new bone formation in abnormal sites [1]. Due to their role in weight-bearing activities, the joints of the lower extremity are most commonly involved in this pathology. CNA of the upper extremity occurs in shoulder most frequently [2]. However, CNA of the hand is quite uncommon. In this study, we aimed to present a diabetic patient with CNA of the right hand after upper extremity trauma.

Case Presentation

A 50-year-old female patient admitted to our hospital with painless joint swelling, movement limitation and deformity complaints on the right hand. Two years ago, she dropped on her right arm and after this trauma, swelling, pain and weakness complaints were developed on her arm. She appealed to a hospital with these complaints and was diagnosed with shoulder dislocation, humeral fracture and fracture-dislocation of the wrist. After plaster cast treatment for 6 weeks, swelling, pain, weakness and movement limitation complaints were in progress and she was admitted to a centre for carrying out physical therapy and rehabilitation program. After physical therapy and rehabilitation program, pain and swelling complaints

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decreased but movement limitation and weakness were in progress. Although movement limitation decreased slightly, she could do her daily works as a farmer by using her right hand predominantly but for skilled movements, she used her left hand. She appealed to our hospital with complaint of movement limitation, painless swelling and deformity on the right hand. The patient had newly diagnosed diabetes mellitus, hypertension, hyperlipidemia, hepatitis-B and chronic bronchitis as systemic diseases. She did not have a knowledge about individuals with these symptoms in her family. No abnormality was detected on rheumatological questioning. There was no pathologic finding on physical examination of systems except locomotor system. Left upper extremity and bilateral lower extremity findings were normal. Although right shoulder flexion was limited at 145 degrees actively and passively, other ranges of motion (ROM) of shoulder were normal. Elbow flexion and extension ranges were normal, but supination and pronation were limited at last 10 degrees actively and passively. Wrist ROM was normal. First metacarpophalangeal joint (MCP) and interphalangeal joint ranges were normal. MCP flexion of 2-3-4 fingers were limited at 40 degrees. Flexion of 2-3-4-5 proximal interphalangeal (PIP) were limited at 80 degrees but extension was normal. Extension of 2-3-4-5 distal interphalangeal (DIP) were limited at last 5 degrees. Flexion of 2-3-4-5 DIP were complete but all the fingers were standing position of flexion (Figure 1).

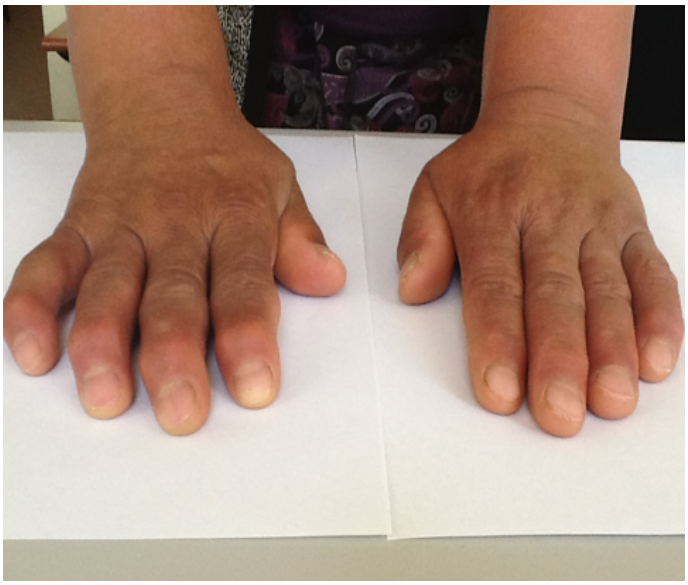

Figure 1. Painless swellings and deformities on the right proximal interphalangeal and distal interphalangeal joints

Although upper extremity motor examination was normal (5/5) around the elbow, wrist and fingers in present ROM, muscle strength of right shoulder abduction and flexion were 4/5. A diffuse hypoesthesia and hypoalgesia was detected on right upper extremity, deep tendon reflexes were normal, and no pathologic reflexes were found. Tinnel's and Phalen's sign tests of right wrist were positive. Hypertrophic, erosive and degenerative changes were detected on DIP and PIP joints of right hand on x-ray but there were no changes on left hand (Figure 2).

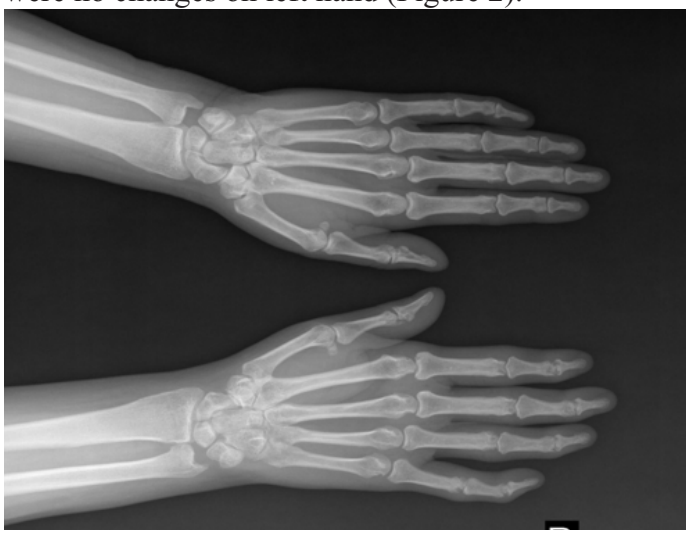

Figure 2. Osteophytes, hypertrophic, erosive and destructive changes on proximal interphalangeal and distal interphalangeal joints of right hand, no degenerative changes on left hand.

There were no considerable changes on the x-rays of shoulder, arm, elbow, forearm and wrist. The results of the patient's blood analysis were associated with diabetes mellitus, hyperlipidemia and hepatitis-B. In addition, serum erythrocyte sedimentation rate and C-reactive protein values were normal. Rheumatoid factor, uric acid, anti-nuclear antibody, extractable nuclear antigens values were normal. Free T3, Free T4, thyroid stimulating hormone, vitamin B12, folate and parathyroid hormone values were normal but 25-hydroxyvitamin D was detected 11.8 ng/mL described as lower. Right mild pan-brachial plexopathy and moderate carpal tunnel syndrome (CTS) was detected on electroneuromyography (ENMG). After these evaluations, the patient was diagnosed as CNA caused by diabetes mellitus, brachial plexopathy and CTS and the treatment was planned in this direction.

Discussion

CNA is a limb-threatening, destructive process that occurs in patients with neuropathy associated with central and peripheral neurological diseases such as diabetes mellitus, syphilis, syringomyelia and peripheral nerve injuries. Diabetes mellitus is the leading cause of CNA and current estimates of its prevalence range from 0.08% in the general diabetic population to 13% in high-risk diabetic patients [3]. In addition, syringomyelia is the leading cause of CNA of the upper extremity, with the shoulder and elbow being the most commonly affected joints [2]. CNA is one of the most destructive complications of diabetes mellitus, leading to subluxation, dislocation, deformity, and ulceration of the foot and other joints. The basic factor in pathogenesis of CNA is lack of sensorial stimulus coming from joint. Deficiency in the sensations of pain and proprioception causes prolonged trauma to joint. Reiterative traumas to joint triggers fibrillation and fragmentation of cartilage and this situation causes formation of loose bodies in the joint space [4]. Despite severe clinical findings, pain is not a disturbing symptom for patients and this is the most important factor for differential diagnosis. However, osteoarthritis, monoarticular and poliarticular diseases, infective artrhopathy, crystal deposition diseases, trauma, hemarthrosis, intermittent arthritis and osteonecrosis should be considered in the differential diagnosis [5]. In our patient, the most distinctive feature is severe joint destruction in DIP and PIP joints of right hand without pain. Our patient had a mild brachial panplexopathy and moderate CTS on the right side, but we evaluated the patient two years after the injury. The patient said that there was no muscle strength on her right arm after injury for a few months. After this duration the muscle strength increased slowly and movement limitations occured in first 6 months after injury on the paretic side, so we thought that there was a severe brachial plexus injury on the right side after injury but a good healing occured on the brachial plexus and muscle strength increased little by little. The patient was diagnosed as CNA because the patient had painless destructive arthropathy on DIP and PIP joints and newly diagnosed and long time untreated diabetes mellitus as a major cause of CNA. In addition, the patient was diagnosed brachial plexopathy and CTS by using ENMG are other causes of CNA. Furthermore, we found abnormal neurological findings on the right upper extremity concomitant to destructive arthropathy. The rheumatological questioning and acute phase reactants were normal and severe destructive arthropathy was detected on radiological images. Interestingly, destructive changes were detected on DIP and PIP joints but there was no change on wrist joint. According to above symptoms and findings, other diseases were excluded, and the patient was diagnosed with CNA associated with diabetes mellitus and peripheral nerve injury. In patients with diabetes mellitus, CNA mainly affects major weight-bearing joints, especially the foot and ankle. CNA rarely affects joints other than the foot and ankle in diabetes mellitus patients and only a very few cases of CNA of the wrist have been reported so far [6, 7]. The explanation of this rarity is the lesser degree of upper extremity involvement due to sensorimotor and autonomic neuropathy in comparison with the lower limb. In addition, CNA affects weight-bearing joints primarily, like the foot and ankle, which are exposed to continuous trauma [6]. The patient used her right hand dominantly and her occupation (farmer) was a risk factor for developing CNA because of constituting micro and macro trauma to the hand. We think that, newly diagnosed and uncontrolled diabetes mellitus and presented nerve injuries caused to reduction of pain and proprioceptive sensation so the trauma did not disturb the patient. Traumatic phase continued and a trauma-inflammation circle occured, so this situation could accelerate the development of CNA. There is yet no specific pharmacological treatment for CNA. Some clinicians also prescribe bisphosphonates in the early stages of treatment, as the bone mineral density of the affected foot is low [8]. Off-loading the affected joint with bracing for at least 2-3 months seems to be essential. Aside from pain management, good glycemic control is also a crucial part of the therapy [9]. Keep in mind that a patient with neuropathy may be unaware of injury to the joint, so patient and family education is so important. Surgery is reserved for severe ankle and midfoot deformities that are susceptible to skin ulcerations and that make braces and orthotic devices difficult to use [10].

Conclusion

Our patient had uncontrolled diabetes mellitus. In addition, a major trauma occurred to the right upper extremity and symptoms and findings were coming out after this trauma so we must keep in mind that major or minor traumas in diabetic patients can

increase the risk of CNA on upper extremity as a complication of diabetes mellitus.

Informed consent

Written informed consent was obtained from the patient for the publication of this case report.

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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A rare complication related to H1N1 infection: Dilated cardiomyopathy

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ABSTRACT

The symptoms and findings of influenza A (H1N1) resemble the symptoms and findings of seasonal influenza and it generally emerges as an upper respiratory tract disease. Although the majority of patients with the influenza A virus recover spontaneously without complications, there have been occasional reports of myopericarditis. However, the most frequent complications have been reported as viral pneumonia and more rarely dilated cardiomyopathy. In this paper, we report a 4-month-old infant, who admitted with shortness of breath, cough, tachycardia and respiratory problems and was diagnosed as having developed dilated cardiomyopathy associated with H1N1.

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Keywords: H1N1, myocarditis, dilated cardiomyopathy

Introduction

The Influenza A (H1N1) virus was first identified in Mexico in 2009 and rapidly spread throughout the world [1]. Clinical findings resemble those of seasonal influenza, such as fever, sore throat, cough, listlessness and myalgia. In children, there may also be vomiting and diarrhea, which are not often seen in seasonal influenza. H1N1 diagnosis is made from nasal secretion or nasopharyngeal specimens samples assayed with the polymerase chain reaction (PCR) [2]. Pneumonia is the most common complication of the infection and this can occasionally lead to central nervous system findings, severe dehydration, renal failure, septic shock and multiple organ failure [1]. The influenza virus is generally self-limiting in healthy children, but even as an acute, complication free disease, it can sometimes result in death because of myocarditis and dilated cardiomyopathy [1]. In this case presentation, attention is drawn to the need to bear in mind H1N1 virus and myocarditis and dilated cardiomyopathy which may develop associated with H1N1 in patients who present with findings of viral respiratory tract infection and unlike the classic course demonstrate a long and resistant course.

Case Presentation

A 4-month-old male infant experiencing shortness

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Table 1. Laboratory findings of the patient.

Laboratory tests	Values
White blood count (K/uL)	11.87
Hemoglobin (g/dL)	12
Hematocrit (%)	30.1
Platelets (K/uL)	239.3
Glucose (mg/dL)	92
Urea (mg/dL)	28
Creatinin (mg/dL)	0.45
ALT (U/L)	16
AST (U/L)	43
Na (mmol/L)	133
K (mmol/L)	3.3
Cl (mmol/L)	106
CRP (mg/dL)	0.19
IgA (mg/dL)	14.8
IgG (mg/dL)	277
IgM (mg/dL)	77
IgE (mg/dL)	7.66
CK MB (ng/mL)	2.13
Troponin I (ng/mL)	0.03
p - ANCA	NEGATIVE
c- ANCA	NEGATIVE
ANA	NEGATIVE
Anti-ds DNA	NEGATIVE
ESR (mm/h)	6
Anti HBS(IU/L)	442.8
RF	NEGATIVE

ESR: Eritrocyte sedimentation rate, RF: Rheumatoid Factor

of breath and tachycardia was to admit another center. As cardiac arrest developed, the patient was transferred to our hospital after intubation. On the direct pulmonary radiograph, bilateral infiltrations were present. The laboratory examination results were normal (Table 1). On the electrocardiogram (ECG), 1st degree atrioventricular (AV) block was observed and there were findings of ST wave depression and left ventricular strain pattern on V3-V6 (Figure 1). Transthoracic echocardiography showed dilatation of the left cardiac chamber, moderate mitral valve regurgitation, and mild aortic valve regurgitation. The left ventricle ejection fraction (LVEF) was 32% and the shortness fraction of 15%. Tests were applied with the consideration of viral respiratory tract infection and viral myocarditis. Treatment was started of antibiotherapy, inhaled salbutamol, inotropic, furosemide and captopril. H1N1 production was determined in the nasopharynx smear taken on admittance. Oseltamivir treatment was started with the consideration that there was cardiomyopathy and the clinical manifestation could be associated with the H1N1 virus.

On the 5th day of the oseltamivir treatment, the body temperature returned to normal, the respiratory problems and clinical manifestations recovered, so the patient was extubated, and the oseltamivir treatment was terminated. On the 15th day of hospitalization, in the clinical observation, LVEF was 40% and at the 6-

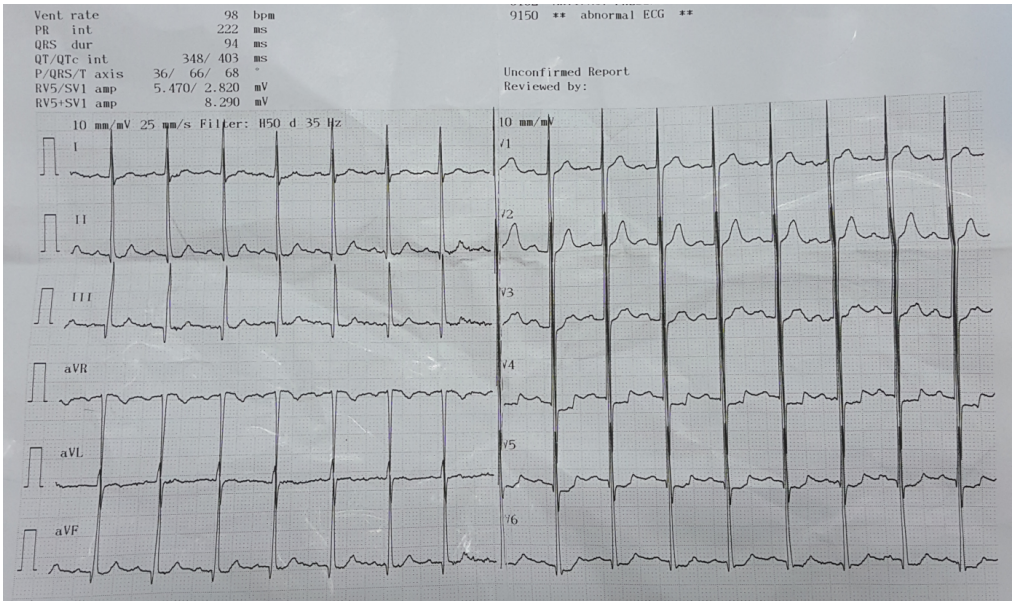

Figure 1. Electrocardiogram shows 1st degree atrioventricular block and findings of ST wave depression and left ventricular strain pattern on V3-V6.

month follow-up examination, LVEF was 50% (Figure 2). The echocardiography findings of the follow-up period are shown in Table 2.

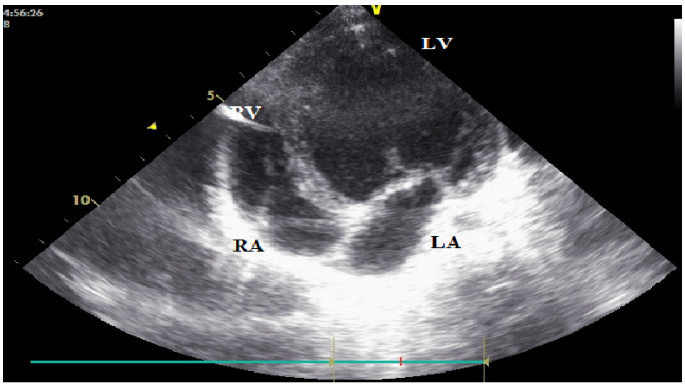

Figure 2. The 6-month follow-up echocardiographic examination. LV = left ventricle, RV = right ventricle, LA = left atrium, RA = right atrium

Discussion

In dilated cardiomyopathy, which is the most frequently seen cardiomyopathy, the left ventricle or both ventricles are dilated, and the heart contractions are reduced. The etiology is most commonly idiopathic followed by viral (coxsackie virus type B, adenovirus, echovirus, influenza types A and B), immune, genetic and toxic causes. In a previous study of 24 patients diagnosed below the age of 2 years, myocarditis was determined in the etiology of 45% of the cases. Influenza type A has been reported to be among the causes of myocarditis [3, 4]. As in some myocarditis cases, the current patient presented with upper respiratory tract symptoms. Tachycardia, tachypnea and cardiac failure, not consistent with fever, are the common findings seen in myocarditis patients. Sinus tachycardia, ST, T-wave changes are seen on ECG, cardiomegaly on telecardiogram, impaired left ventricle function on echocardiography, and elevated CKMB-Troponin levels [5, 6]. Although a definitive diagnosis of myocarditis can be made from myocardial biopsy, there must be an awareness of the risks of taking a biopsy from a patient with myocarditis [7]. While supportive treatment is generally sufficient in myocarditis, in patients presenting with dilated cardiomyopathy, as in the current case, treatment must be directed to congestive heart failure. H1N1, which often presents with influenza-like findings, is more severe in patients aged below 2 years [8]. Although very rare, this may be due to dilated cardiomyopathy, as in the current case.

The pathophysiology of cardiomyopathy associated with influenza is not yet fully understood. In severe influenza infection, vascular permeability increases with cytokine mediation and endothelial cell damage contributes to cardiac dysfunction [9]. Martin *et al.* [10] reported that there was systolic dysfunction in approximately 5% of patients and a return to basal values in 60% of these. This showed that although systolic dysfunction is rare, it can be corrected. As in the current patient, severe complications such as dilated cardiomyopathy thought to be related to H1N1, can be reduced with the use of oseltamivir and similar antiviral agents [11]. In patients presenting with symptoms of upper respiratory tract infection, who are followed up because of the subsequent development of respiratory problems and lower respiratory tract infection, H1N1 virus should be considered in the etiology.

Conclusions

Although cardiac complications associated with H1N1 virus are rare, myocarditis and dilated cardiomyopathy should be kept in mind, especially for patients with a complicated course. The necessary interventions and treatments should be applied to the

Table 2. The echocardiographic findings at follow-up period

	EF (%)	SF (%)	LVEDd (mm)	LVESd (mm)
1st day	32	15	59	50
15th day	40	19	50	40
3rd month	42	21	47	37
6th month	50	26	45	33

EF = ejection fraction, SF = left ventricular shortness fraction, LVEDd = left ventricular end-diastolic diameter, LVESd = left ventricular end-systolic diameter

patient with a multidisciplinary approach.

Informed consent

Written informed consent was obtained from the patient's family for the publication of this case report.

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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