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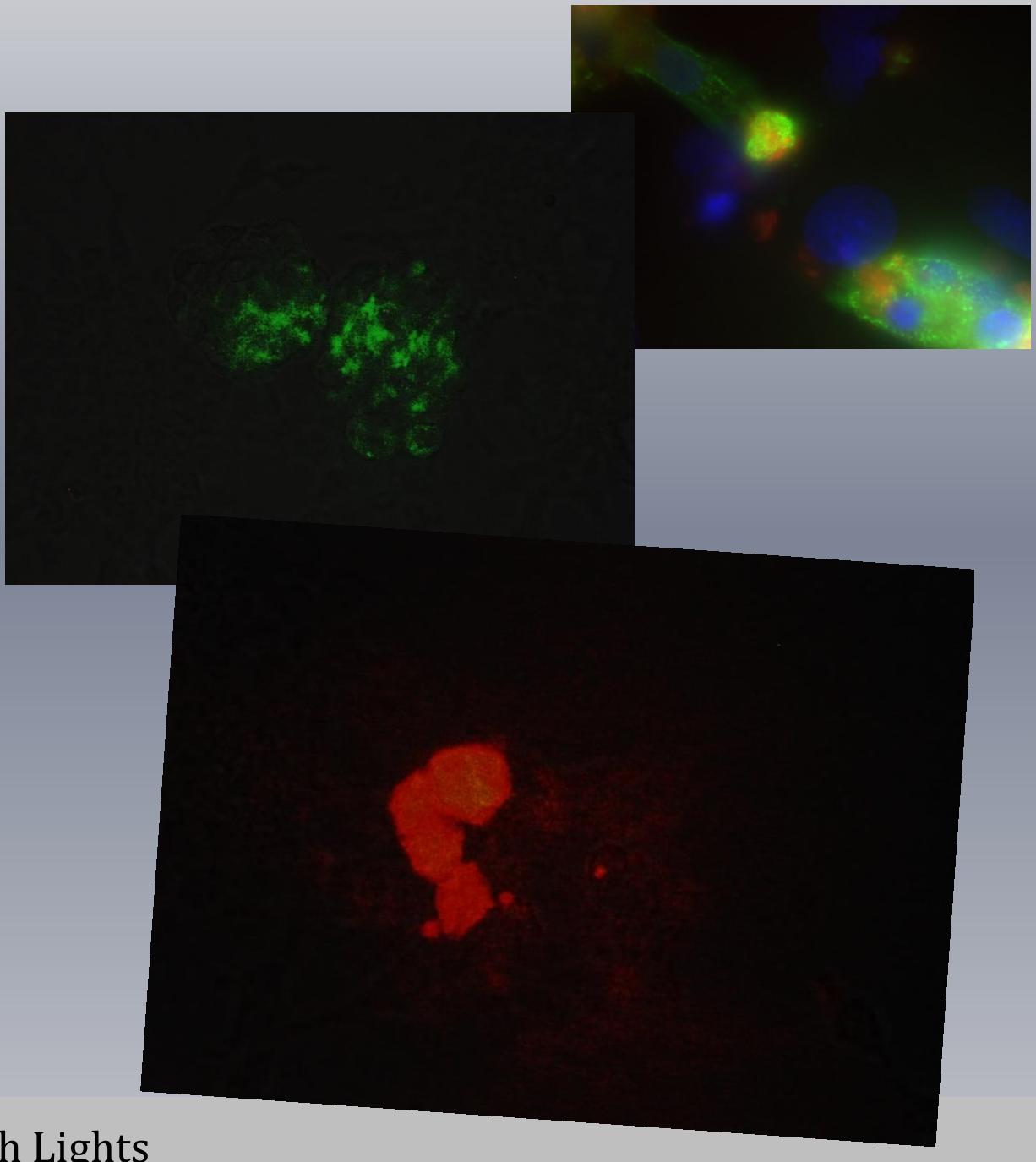

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Review Article Doi: 10.17546/msd.55299

Effect of heavy metal and some trace element levels on radiotherapy taken breast cancer patients

Halit Demir[1]*, Canan Demir[2]

Abstract

Objective: The aim of this article is to research the effects of radiotherapy on trace elements and heavy metals in patients with breast cancer. Breast cancer is a common disease worldwide. Breast cancer risk increases with age and occurs at much higher levels in postmenopausal women. During radiation therapy for the treatment of breast cancer, damage to tissue may result. Depending on the treatment technique applied, other areas apart from the treatment area may be affected. For example, the lungs may be negatively affected, resulting in decreased lung capacity. Consequently, free radicals may be formed as a result of oxidative stress incurred due to insufficient lung capacity

Plan and design: In this review article, approximately 110 articles were consulted.

Result: Radiotherapy may cause damage to or loss of tissue, and may have negative effects on trace element levels. Consequently, levels of heavy metals and trace elements may be altered during radiotherapy.

Conclusion; An increase in heavy metals leads to greater oxidative stress, which is associated with a higher risk of cancer. Normal levels of Zn may also decrease the risk of cancer.

Keywords: trace elements, heavy metals, radiation therapy.

Introduction

Breast cancer is a common disease worldwide. Breast cancer risk increases with age and occurs at much higher levels in postmenopausal women. Among women, breast cancer is the second most common type of cancer resulting in death, after lung cancer.

Radiation therapy can be used to treat all types of solid tumors including brain, breast, stomach, larynx, esophagus, and other head and neck cancers. Postsurgical radiotherapy can be used in the adjuvant treatment of breast cancer to prevent local recurrence. Radiotherapy is also used in order to prevent recurrence after a local recurrence, thus showing the importance of treatment modality.

Trace elements play a very important role in human health, even though they are found in very minute amounts. Levels of Cu and Mg before and after radiotherapy in breast cancer patients have been shown to be statistically significant when compared with a healthy control group [1]. Serum Cu levels were found to be lower in lung cancer patients than in healthy people [2]. Levels of Ni were found to be increased in 15 patients with breast cancer [3].

Manganese and zinc, which are necessary for the superoxide dismutase enzyme system to function, are known to inhibit radiation-induced toxicity. In a study on colorectal cancer patients, varying levels of Fe, Cu, Mn and S were found [1-4]. Levels of Na, Mg, Ca, Se, Rb and Mo were observed to decrease in the plasma of lung cancer patients undergoing radiotherapy. However, levels of Al, S, V, Fe, Cu, Al, Co, Co, Mn, Hg and Pb increased [5]. While cadmium (Cd), cobalt (Co), antimony (Sb), barium (Ba), mercury (Hg) and lead (Pb) levels were found to increase prior to radiotherapy, the levels remained constant following radiotherapy [5]. In a study conducted with patients with locally advanced lung cancer, head and neck cancers, and cervical cancer who underwent radiotherapy, Se levels were examined before and after radiotherapy. Se levels decreased in response to therapy, and the rise in SA levels was interpreted as an enhanced response [6].

Recently, Zn levels in breast cancer patients were found to be significantly higher than in the control group [7].

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However, in another study, no significant difference between Zn levels inbreast cancer patients and the control group was observed [8]. In the literature, levels of Fe, Cu, and Zn are considered biomarkers of breast cancer [9]. Cu levels in breast cancer patients were also found to be higher than in the control groups in two separate studies [8, 9]. Cu and Zn levels have been observed to increase in breast cancer patients compared to control groups [10]. The importance of Zn as a carcinogenic agent is still subject to controversy. Zn may influence some cancers in several ways [11]. Deficiencies of trace elements such as Cu and Mg have been implicated in various reproductive disorders including infertility, miscarriage, cancer of the reproductive organs, pregnancy-induced hypertension, placental abruption, premature rupture of membranes, still births and low birth weight [12]. Although little research on the interaction between Co and cancer has been published so far, a few studies which have been published are intriguing. Exposure to Co has been shown to convert human osteoblast-like cells into the tumorigenic phenotype and to activate the expression of genes related to cancer [13, 14]. Cd is a very toxic heavy metal and, unlike organic compounds, it is not biodegradable and has a very long biological half-life [15]. In one study, increased Cd levels were found in the serum of lung cancer patients [16]. Usually, carcinogenic elements can act as epigenetic carcinogens and carcinogenic metals can be genotoxic [17]. In one study, significant differences in the levels of Fe, Cu and Zn, were detected in some types of cancer [18]. Fluctuations in the concentrations of elements such as Zn, Cu, Mg, Pb, Mn, Cd, Co and Fe were also detected at significant levels in the blood of ovarian cancer patients [19]. Significant changes in serum levels of trace elements have been observed in prostate cancer patients [20]. Zn concentrations in ovarian and cervical cancer patients have been reported at lower concentrations with respect to control groups [21, 22]. Zn may be protective against lung cancer. In addition, it was found that low levels of zinc could induce the pathogenesis of lung cancer. Lower levels of zinc might have an important role in the pathogenesis of lung cancer [2]. In one study, levels of Cd and Pb were found to be increased in patients with malignant glioma cancers [23]. In another study, it was also shown that concentrations of Cd and Pb in the serum samples of patients with renal cancer were increased compared to the control group [24]. Serum trace elements were significantly lower in breast cancer patients compared to controls in one study [25]. In another study, Zn, Cu, Se, and Fe concentrations were high in cancer patients. In addition, in the same study, it was shown that the changes in trace element levels in serum and tissue might be of benefit as biomarkers during the initial plastic process [26]. Serum zinc levels were unchanged in patients with early breast cancer and benign breast disease [27]. Low selenium levels were detected in patients with diseases such as various cancers, muscular dystrophy and heart disease [28]. According to some studies, various trace elements were thought to play a role in carcinogenesis of breast cancer [29, 30]. Fe levels in breast cancer patients have been reported at higher concentrations with respect to control groups [7, 8].

The implementation of proper radiotherapy in the treatment of breast cancer can significantly prolong survival time in patients [31]. In one study, high Cu / Zn ratios following radiotherapy was found to be potentially useful in assessing possible improvements in breast cancer patients [10]. Although there have been some studies on breast cancer carcinogenesis, the role of trace elements has not been fully clarified yet [32]. For women in the United States, breast cancer continues to be one of the most common cancers [33, 34]. In one study, cadmium was found to cause early puberty and possibly increase the risk of breast cancer [35]. In a recent study, cadmium was reported to cause DNA damage in breast cancer patients [36]. Lead levels in breast cancer patients' tissue were significantly higher in both malignant and benign tissue [37]. In a study of 20 breast cancer patients, high nickel levels were found [38]. In another study, chromium levels were found to be significantly higher in breast cancer patients than in the control group [39]. Breast cancer patients were found to have significantly higher iron levels in another study [40].

Result

During radiation therapy for the treatment of breast cancer, damage may occur to tissue, even to tissue which is not located in the treatment area, depending on the treatment techniques applied. Radiotherapy may also cause loss of tissue, and may have negative effects on trace element levels. Consequently, levels of heavy metals and trace elements may be altered during radiotherapy. An increase in heavy metals leads to greater oxidative stress, which is associated with a higher risk of cancer. Normal levels of Zn may also decrease the risk of cancer.

Conclusion

As a result; radiotherapy for breast cancer should be examined, when the treatment of oxidative damage of the lung volume is controlled.

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Conflict of Interest: The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Why epidural blood patch and postdural pain headaches

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Abstract

Objective: Spinal anesthesia has some complications such as intravascular injections, nerve injuries, hypotension, bradycardia and dural ruptures. When puncture is performed on dura or araknoid, there is a risk of post-dural-puncture headache.

Material and Methods: 16003 patients, who were operated at the Erzincan State Hospital and Erzincan Mengücek Gazi Education and Research Hospital between 2004 and 2011 were involved in this study. Epidural blood patch was applied on 159 patients complaining of post-dural-puncture headaches. 15 ml of the autologous blood was given to the epidural region in the surgery room for patients which had epidural blood patch applied. Epidural blood patch was applied 2 days after the dural injury

Results: 72 females and 67 males were involved in the study. Symptoms of post-dural-puncture headache disappeared within minutes immediately after the process. After the first application of epidural blood patch, 156 patients felt relaxed. 3 patients had a relief after the first application, but their symptoms relapsed, and a second injection was performed 24 hours after the first one. Following the second epidural blood patch, none of the patients reported any headaches. No complications emerged during the procedure in the patients. The patients were discharged 2-3 hours after the epidural blood patch application.

Discussion: Epidural blood patch is a treatment method with lower risks of complications, lower costs and high success rate for post-dural-puncture headache patients. It is advised especially after the C-section, for preserving mother-baby communication.

Key words: Blood Patch; Epidural; Postdural; Pain; headache; Anesthesia, Spinal

Introduction

Spinal anesthesia has some potential advantages over general anesthesia and it has been widely and successfully used for nearly 100 years, especially in surgeries of lower abdomen, perineum and lower extremities (1). Some major advantages of regional anesthesia are the continuation of patient's spontaneous respiration, preservation of oropharyngeal reflexes, postoperative analgesia and shorter length of hospitalisation (2,3). With new local anesthetic drugs and spinal needles introduced, complications are minimized and more professionals prefer this method (4).

Spinal anesthesia is an alternative to general anesthesia in most cases. It can be used simultaneously with general anesthesia, or postoperative for analgesia, acute and chronic pain treatment. Today, most of the C-sections attempts are also carried out with the epidural or spinal anesthesia (5). It was shown that with an appropriate approach, neuroaxial anesthesia methodologies are highly safe, but there can be some complications emerging during and after the procedure. Some of these complications are intravascular injections, nerve injuries, hypotension, bradycardia and dural rupture (6,7). When puncture is performed on dura or araknoid, there is a risk of Post-dural-puncture headache (PDPH). Post-dural-puncture headache is the most common complication of the regional block anesthesia and it is an important condition caused by the leakage of the cerebral spinal fluid (CSF) from the hole opened by the needle during dura puncture and related to CSF pressure(8).

The international headache society defines PDPH as a bilateral headache developing within 7 days after the lumbar puncture and disappearing in 14 days (9), while Vandam and Dripps (10) defines it as pain which can affect both sides of the neck and shoulders even though it is generally in frontal and occipital regions.

The aim of this study is to share our clinical experiences on Epidural patch as a treatment procedure in patients with PDPH

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Material and Methods

This retrospective study has been approved by ethical committee of the Erzincan University, Faculty of Medicine. 16003 patients, who were operated in the Erzincan State Hospital and Erzincan Mengücek Gazi Education and Research Hospital between 2004 and 2011 were involved in this study. Patients complaining from PDPH had nausea and back/neck pain as well as headaches. These symptoms were increasing, especially when the patients were standing. Epidural Blood Patch (EBP) was applied on 159 patients' suffering from PDPH. Spinal anesthesia was applied on 72 of these patients, while combined regional anesthesia was applied on 87 of them. Patients were aged between 19 and 74. Patients were involved in the study after operations in inguinal hernia, C-section, anal region diseases and urological and lower extremity orthopaedics. Patient Demographic Features are given in Table 1.

The epidural patch was applied in the surgery room to all patients. After taken to the surgery room, the patients were monitored, veins were opened with 18 G branule from antecubital fossa and 500 ml crystalloid was given. When the patients were in a sitting position, skin was sterilized with povidone iodine. After local anesthesia, process was started in L4-5 range, with loss of resistance method, using 18G Tuohy needle normal saline (N/S). Subarachnoid range was entered 4.5 cm away from skin. When the injector leaves the epidural needle, CSF flow was seen, and it was confirmed as CSF with flow rate and temperature after that, epidural needle was pulled until CSF flow stopped and the pulled distance was confirmed as epidural range with N/S injection aspiration method. Patient's antecubital zone was sterile cleaned with povidone iodine. 20 ml autologous blood was taken with a 20 ml IV injector and 15 ml blood was given to the epidural range from epidural range Tuohy needle.

Success of EBP was measured as total relief (disappearing of all symptoms), partial relief (being able to clinically perform daily activities) or failure (persistence of serious symptoms).

Results

72 females and 67 males have been involved in the study. Surgeries and anesthesia's of the patients are given in Table 2.

27 G Quinke spinal needle was used on all 87 patients spidural. Anesthesia was performed while for spinal anesthesia, 25 G Quinke was used for 30 patients, 27 G Quinke was used for 25 patients, 29 G Quinke was used for 10 patients and 22 G Quinke was used for 7 patients, All patients were discharged 24 hours after the procedure.

According to the patients' records, EBP was applied to 159 patients with VAS scores between 7 and 9. Patients with VAS scores 4-5 were conservatively followed (iv liquid replacement, 3000 ml paracetamol-cafein combination or analgesic treatment with NSAI drugs). 15 ml autologous blood was given to epidural region in the surgery room and to the patients, EBP was applied. EBP was applied 2 days after the dural injury. Symptoms of PDPH disappeared within minutes immediately after the process. After the first application of EBP, 156 patients felt relaxed. 3 patients had a relief after the first application, but their symptoms relapsed, and a second injection was performed 24 hours after the first one. Following the second EBP, all complaints of these patients disappeared. No complications emerged in the patients. Patients were discharged 2-3 hours after EBP application.

Table 1: Patient Demographic Features

	COMBINED (spidural)	**SPINAL**
C-section	4105	2198
Lower abdomen surgery(ing. herni, Umb. Her. P.sinüs- hemoroid)	3178	1538
Orthopedics(meniscopathy)	2201	1642
Urological cases (BPH-Ureter stone- varicosele)	3424	923
Gynecologic cases (histerektomi)	489	410
TOTAL	9292	6711

Table 2: The surgeries of post-dural puncture headache

	COMBINED (Spidural)	SPINAL	Age Ratio
Section	47	28	27
Lower abdomen surgery	13	14	32
Orthopaedics	9	16	31
Urological cases	14	9	33
Gynaecologic cases	2	4	41
Total	85	71	29

Discussion

Even though spinal anesthesia is the most common regional anesthesia methodology, most of the clinicians and physicians had negative feeling towards it and were aversive due to the risks of infection, spinal neurotoxicity, post-spinal headaches and life-threating complications (11). PDPH, caused by leakage of CSF from the hole in dura opened by the needle used in spinal anesthesia and related to CSF pressure, has many negative consequences and it is a serious condition. The most important factor in its emergence is considered as needle type and thickness (12). PDPH incident varies between 0% and 37% depending on needle type and size (13). As the diameter of the needle increases, risk of the headache occurring also increases (14).

There are many studies showing that pen-edged and small-diameter needles can decrease the PDPH indicence (15). Research on durameters with electron microscopy has shown that pen-edged needles causes more damages with respect to sharp-edged needles. Pen-edged needles are also causing irregular rupture and following inflammatory reaction, and less CSF leakage with respect to the sharp-edged needles cutting in U shape (16). Westbrook et. al. (17) shown that pen-edged needles cause less CSF loss and this is revelant with the needle design

Different studies show that the PDPH incidence is 40% with 22 gauge needle, 25% with 25 gauge needle (18,19), 2-12% with 29 gauge needle and 2% with 29 gauge needle (20,21). Jeanjean et. al. found PDPH incidence as 0.08% in their study with 24 gauge needle (22) and Despond et. al. found incidence as 9.3% with 27 gauge needle (23) and Frenkel et. al, found incidence as 3.5% with 25 gauge needle (24). In our study, PDPH was observed in 5.8% of our patients. PDPH incidence was 5.8% with 22 gauge quincke neede, 10.1% with 25 gauge quincke neede, 5.1% with 27 gauge quincke neede and 1.9% with 29.

We believe that success of epidural patch is directly related to the proximity of blood to the injection puncture region. Injection in the same space is advised, even though not necessary.

If the same spot cannot be used for any reason, using the space below is advised because there is a possibility of blood diffusion in epidural space. Thus, when there is more than one puncture, the lowest puncture region should be used for puncture region injection (25).

Hypotension and bradycardia are common side effects of spinal anesthesia, these situations are easily overcomed by the anesthetist so these side effects do not create a burden and distress in the patient for a long time. However, severe headaches which have been observed in 12-24 hours postoperatively due to dural injuries, can seriously affect patients' comfort as well as mobilization.

Epidural blood patch to treat postdural headaches is known as the gold standard in the literature. Because the epidural blood patch is an invasive method and causing a second dural injury, this method does not seen much interest to the anesthesiologists. Although the continued headache, conservative treatment is continued to postoperative 48 hours.(26). In our experience, conservative treatment did not shorten the duration of the postdural headache and this time were approximately 7 to 10 days longer. When applied by an experienced anesthesiologist, epidural blood patch is reduced to a minimal complications ratio; and it has been found to provide a radical improvement in a very short time in the treatment of postdural headache.

Hospitalization might be necessary for monitoring patients in case of headaches related to cerebrospinal fluid leakage after C-section. This might cause early dissociation of mother and baby (27). EBP can be used to prevent cerebrospinal leakage and preserve mother-baby bond.

Conclusion

EBP is a treatment methodology with lower risk of complications, lower costs and high success rate for PDPH patients. It is advised especially after C-section, for preserving mother-baby communication.

Conflict of Interest: The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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The investigation of relationship between adrenomedullin vascular growth endothelial factor in obese and calorie restricted rats

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Abstract

Objective: Obesity and overweight are the most frequent chronic medical problems, and the increasing prevalence of obesity is a worldwide phenomenon. According to the data of World Health Organization (WHO) obesity affects over 300 million people. This study reports the effects of adrenomedullin (AdM) in obesity, due to its functions as arranging vascular endothelial function, and adjusting adipogenesis.

Material and Methods: Rats were separated into five groups randomly. Tissues were collected when the rats of obesity groups were gained 20% of their weights, and when the rats of calorie restricted groups were lost 20% of their weights. Then, AdM and vascular endothelial growth factor (VEGF) levels were measured.

Results: We showed that AdM application increased VEGF in all tissues of calorie restriction+AdM group, and the most spectacular effect of AdM injection was the quite elevated VEGF level of white adipose tissue (WAT) in calorie restriction+AdM group, because these individuals need passive fat depots (WAT) more than biologically active fat tissue (brown adipose tissue: BAT). Other remarkable level was in obese+AdM; AdM application lowered VEGF level by diminishing WAT depots. Contrary to this, AdM application increased VEGF levels of BAT in obese+AdM group.

Conclusion: There is a synergy between AdM and VEGF. AdM regulates the vascularization of tissues (WAT or BAT) according to the individual's requirement. Consequently, AdM may have a protective effect towards obesity, and according to metabolic situation of individual's adipose tissue, AdM application may provide consumption of energy by increasing vasculature of BAT in obese individuals.

Key words: Adrenomedullin, obesity, WAT, BAT, angiogenesis

Introduction

WHO defines obesity as an abnormal or excessive fat accumulation that disrupts health (1). Obesity is a complex, chronicle, multifactorial disease related to the interaction of genetic and environmental factors, and appears to be an important global health problem (2). Overweight represents the person weights over from standards according to height and age; obesity represents the excessive body fat. WHO developed an international classification for obesity. Body mass index (BMI) between 25-29,9 kg/m2 reflects overweight; 30-39,9 kg/m2 reflects obese; 40 kg/m2 and upper reflects morbid obesity. The risk of complications caused by obesity is increased with BMI over 25 kg/m2 (3). Obesity is in collaboration with a number of diseases including hypertension, dyslipidemia, type II diabetes mellitus, coronary artery disease, stroke, gallbladder diseases, sleep apnea, respiratory problems, breast cancer, prostate cancer, and colon cancer. There is also an increased relationship between elevated weight and mortality related to all reasons (4,5). AdM is a vasodilatator peptide consisting of 52 amino acids which was firstly discovered in the tissue isolated from pheochromocytoma in 1993 (6). AdM is mainly synthesized in medulla, and also synthesized in many tissues such as myocardium, lungs, central nervous system, endothelium, vascular smooth muscle cells, and adipose tissue (7). AdM is a biologically active peptide that has various effects including vasodilatation, the regulation of vascular endothelial function, inhibition of cardiovascular alteration, adjusting adipogenesis, and decreasing insulin resistance (8). There is also AdM in circulation; the levels of plasma AdM are found increased in hypertension, obesity, heart failure, acute myocardial infarct, and atherosclerotic vascular disease (9, 10). Because of its biological functions, it is assumed that AdM takes part in the mechanisms act against development or progress of metabolic or cardiovascular diseases (11-13).

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Angiogenesis, or the formation of new vessels from existing vessels, plays the essential role in during and after development, adult life, several physiological (i.e. formation of corpus luteum), and pathologic conditions such as malignancy and inflammation. This event is rather important in physiological conditions (14, 15). Angiogenesis takes place in wound healing, development of placenta after fertilization, regeneration of inner stratum of uterus after menstruation (16). Angiogenic stage is a complex multistep process including the sequential decomposition of basic membrane, migration and proliferation of endothelial cells, and the self-organization of endothelium cells for forming capillary lumen followed by inhibition of endothelial proliferation, the new formation of basic membrane, and the accumulation of periendothelial cells (17, 18). Hence they are genetically stable and easily accessible via circulatory system, endothelial cells are accepted recently as the most attractive targets for treatments that aim to increase and inhibit angiogenesis (19, 20). Angiogenesis is very important for growing, development, and repairing of all tissues (16). Adipose tissue, particularly BAT, due to each adipocyte is surrounded by capillaries, probably is the most vascularized tissue in the body. It is actually demonstrated that angiogenesis has a considerable role in regulation of adipogenesis and obesity. Obesity related disorders such as obesity and diabetic complications, cardiovascular disorders and malignancies accompany pathological angiogenesis (21). Although inhibiting angiogenesis of adipose tissue was suggested as the first treatment approach of obesity, this concept now contradicts with the paradox that energy expenditure also may require angiogenesis (21, 22). Development of BAT for prevention of obesity is particularly correct. Therefore, of which negative or positive angiogenesis regulators can be used for obesity treatment is ambiguous. This situation should be related to the metabolic state of adipose tissue of angiogenesis regulator treated to individual. If the angiogenic vessels of metabolically active adipose tissue (BAT) are increased, further energy will be expended. But on the contrary, in obese individuals who have massive metabolically inactive WAT, the inhibition of angiogenesis may be more advantageous (23). Also in this study, by setting forth the thought that angiogenesis may take part in increasing the function of BAT, whether additional AdM treatment to the organism have or not any effect has been investigated

Material and Methods

A total of 60 female 12 months old Wistar rats weighting 185-255 g were used in the study. The rats were purchased from Inonu University Laboratory Animal Reproduction and Research Center (Malatya, Turkey) and were housed in cages in a special room at the temperature of 22 ± 2°C, humidity of 55% ± 5%, and a 12/12-hour light/dark cycle. The experiment was conducted under the protocol approved by the Inonu University. All procedures involving rats were conducted in strict compliance with relevant laws, the Animal Welfare Act, Public Health Services Policy, and guidelines established by the Institutional Animal Care and Use Committee of the university. Rats except obesity groups consumed standard diet and all rats consumed tap water ad libitum. The rats were weighed every week and at the end of the study. All rats were randomly assigned to five groups (n=12): Group 1 (Control)-the control group received standard chow, Group 2 (Obese)-the obese group consumed high fat diet (HFD) consisting of 40% calorie as fat, Group 3 (Obese + AdM)-rats consumed HFD and were treated AdM, Group 4 (Calorie restriction)-rats consumed 20% less calorie from the standard died, Group 5 (Calorie restriction + AdM)-the calorie restriction group treated AdM (24-50). AdM (Phoenix Adrenomedullin) was dissolved in distillated water, and injected to the rats intraperitoneally in a dose of 2.5 nmol/kg for four days. Rats were anesthetized intramuscularly injection of 1500 µl/kg ketamine and 500 µl/kg xylazine.

Collecting and homogenization of liver, lung, brown, and white adipose tissues

After perfusion, rats are euthanasied by removing heart. First, a piece of lung, then, a piece of liver was collected. Retroperitoneal WAT was collected by removing intestine. BAT was collected by opening dorsal of rat. Tissues were rinsed with serum physiologic, and then wrapped with labeled aluminum folio, and immediately put into liquid nitrogen. At the end of the dissection, tissues were removed from liquid nitrogen, and then stored at -40 °C until assayed. Tissues were weighed for homogenization by putting into tarred microcentrifuge tubes. 2 mM PBS buffer (pH 7.3) up to ~20 folds of tissue (500 µl PBS buffer to ~0.025 g tissue) was added. Tissue in the microcentrifuge tube was sliced into smaller pieces with scissor. It was homogenized 20 seconds with ultrasonificator (Bandelin Sonopuls) in ice cold. Homogenized tissues were stored at -40℃, and centrifuged for 20 minutes at 1500 rpm before detection.

Biochemical analysis

AdM and VEGF concentrations were assayed by Enzyme-Linked Immunosorbent Assay (ELISA) method using commercial kits according to manufacturer's instructions. AdM levels were detected with Rat Adrenomedullin (ADM) ELISA Kit CK-E30105 (Hangzhou Eastbiopharm Co., Ltd.), and VEGF levels were detected with VEGF ELISA Kit EK0540 (Boster Biological Technology Ltd.) at 450 nm via microplate reader (BioTek® Instruments, Inc., Eon) in homogenate samples of liver, lung, white, and brown adipose tissues. Standart graphics were drawn

according to the kits' protocols, and the AdM and VEGF levels were calculated by using standard graphics. GraphPad was used to create all graphs, and for calculation.

Statistics

The results were expressed as means ±SEM. Paired T test was performed for detecting diversity between groups, and values of $p<0.05$ were considered to be statistically significant. The statistical analysis was carried out using SPSS for Windows Version 15.0.

Results

AdM and VEGF levels were measured in liver, lung, white, and brown adipose tissues of all groups. AdM and VEGF levels are shown in Tables 1 and 2. AdM is mainly synthesized in medulla, and also synthesized in many tissues such as myocardium, lungs, central nervous system, endothelium, vascular smooth muscle cells, and adipose tissue (7). It is clear that the essential physiological function of AdM is vasodilatation in both systemic circulation (6, 24, 25) and pulmonary stratum (26). In our study, there were significant differences between control group and other groups of AdM levels of liver tissues ($p<0.05$). Control group AdM levels were higher than other groups. We can say that liver AdM levels are sensitive to dietary intake, maybe because of the changes in vasodilatation. AdM can have a role as a circulating hormone, and also can involve in the regulation of cardiovascular system, renal functions, and blood pressure as an autocrine-paracrine mediator (27). AdM is a biologically active peptide that has various effects including vasodilatation, the regulation of vascular endothelial function, inhibition of cardiovascular alteration, adjusting adipogenesis, and decreasing insulin resistance (8). It is indicated that AdM specific binding sites are mostly found in lung tissue (28). AdM levels of lung tissues were found higher in obese+AdM group, but lower in obese group than control group ($p<0.05$), so AdM application increased AdM level in obese+AdM group. Obesity is usually in collaboration with hypertension. Because AdM also has a detractive role in pulmonary hypertension, it can cause protective effect in obese+AdM group. The levels of plasma AdM are found increased in hypertension, obesity, heart failure, acute myocardial infarct, and atherosclerotic vascular disease (9, 10).

After high fat diet, adipose tissue and plasma AdM concentrations increase with the rise of body weight (13). WAT AdM levels were higher in obese, calorie restriction, and calorie restriction+AdM groups than in control group ($p<0.05$), but interestingly no significant difference was found between control and obese+AdM group ($p>0.05$). The BAT AdM level in obese and calorie restriction+AdM groups were lower than control group, but AdM application to the obese group caused elevation according to the obese group ($p<0.05$). Because of its biological functions, it is assumed that AdM takes part in the mechanisms act against development or progress of metabolic or cardiovascular diseases (11-13). Shibasaki et al. showed that AdM mRNA levels of epicardial adipose tissue in individuals with coronary artery disease were high, and they suggested that this could have a protective effect against the disease (29). When the AdM treated obesity group is compared with obesity group; it can be seen that AdM levels of WAT, BAT and liver reach near to the control group level. We suggest that damages caused by obesity can regress by AdM treatment (Table 1).

VEGF or VEGF-A is accepted to be the main factor which takes part in regulation of angiogenesis (30). VEGF-A is the most potent proangiogenic factor defined until now (31). Measuring this parameter gives knowledge about vascularization of the tissue. In this study, VEGF levels of liver in control group were lower than in obese group, and VEGF levels of obese+AdM group were higher than calorie restriction group, but lower than calorie restriction+AdM group ($p<0.05$).Liver VEGF levels were significantly different between all groups ($p<0.05$). The most spectacular VEGF level in WAT was in calorie restriction+AdM group; it was extremely higher than other groups ($p<0.05$), and the other remarkable level was in obese+AdM; it can be easily seen that AdM application lowers VEGF level by diminishing WAT depots ($p<0.05$). Contrary to this, in BAT, AdM application increased VEGF levels of obese+AdM and calorie restriction +AdM group ($p<0.05$), and of course levels were higher in obese+AdM group than calorie restriction+AdM group. AdM activates VEGF receptors in vascular endothelial cells (32). Evans et al. have showed synergy between AdM and VEGF in women have endometrial cancer (33).

Table 1: Adrenomedullin levels (ng/l)

Groups	Liver	Lung	WAT	BAT
Control	439.32±18.12	350.72±11.23	235.94±6.04	323.53±11.86
Obese	286.63±16.88	320.96±12.60	296.10±4.73	228.34±19.05
Obese + AdM	355.64±6.54	439.70±11.37	246.95±6.42	306.44±7.88
Calorie Restriction	309.73±11.13	370.40±16.40	333.2±22.09	353.68±13.15
Calorie Restriction + AdM	268.20±20.37	355.52±9.22	346.03±7.27	285.86±3.21

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Table 2: Vascular endothelial growth factor levels (pg/mL)

Groups	Liver	Lung	WAT	BAT
Control	11601.27±391.98	7279.38±3.65	852.26±90.85	902.81±8.57
Obese	12569.20±177.64	2983.48±188.87	471.42±7.61	408.77±19.18
Obese + AdM	11753.90±466.39	2589.67±22.45	160.14±17.48	7222.72±139.38
Calorie Restriction	7991.21±75.51	1685.31±169.41	522.74±1430	529.85±11.73
Calorie Restriction + AdM	18441.87±941.14	8105.59±306.57	5121.68±154.84	2227.49±122.86

Actually, VEGF levels of BAT are further higher than WAT (34). Our study supports this data in all groups except obese group. BAT VEGF levels were higher in obese+AdM and calorie restriction+AdM groups, but lower in obese and calorie restriction groups than control group ($p<0.05$). We can say that AdM injection increased VEGF levels thereby the vascularization of BAT which helps the energy expenditure in obese+AdM group, so AdM can be used against obesity (Table 2).

Morphologically it can be easily seen that AdM application significantly increased WAT depots of calorie restriction+AdM group, and BAT depots of obese+AdM group (Figures 1, 2).

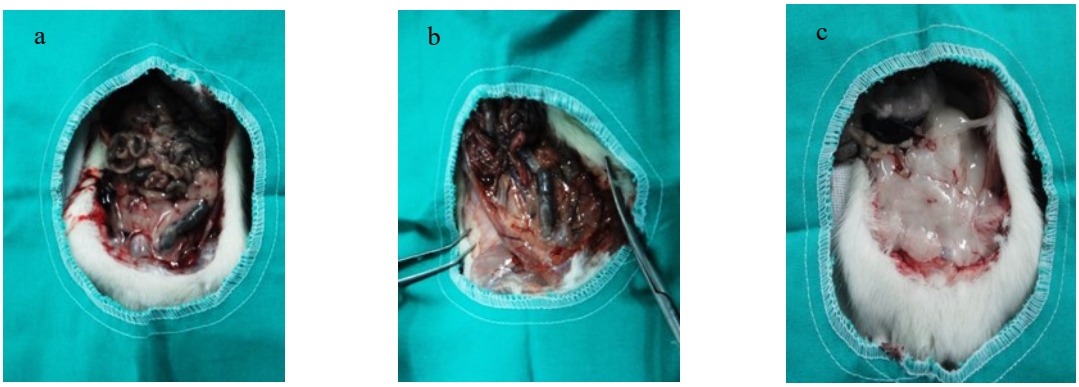

Figure 1: Abdominal white adipose tissue (a) control (b) calorie restriction, and (c) calorie restriction + AdM groups

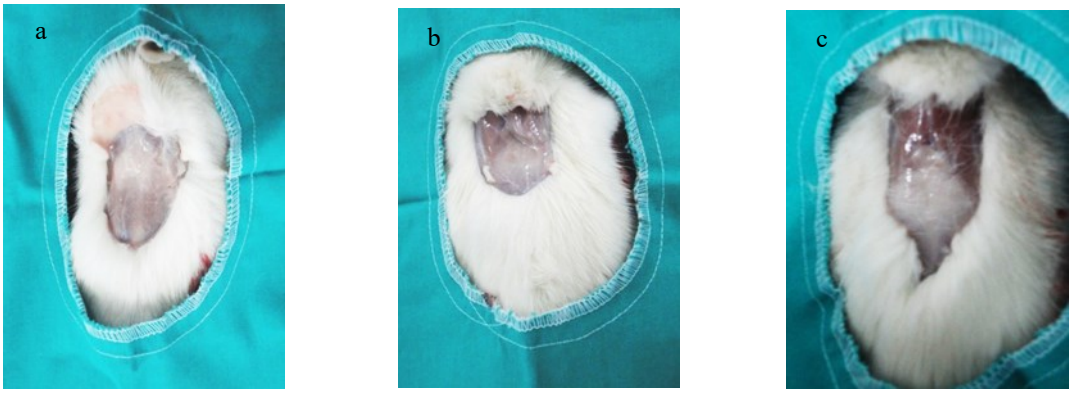

Figure 2: Interscapular brown adipose tissue (a) control, (b) calorie restriction, (c) obese + AdM groups

Discussion

Differences are seen between angiogenic factor levels according to the dietary intake, and we also showed that there are even differences of levels between tissues in obesity and calorie restriction groups. There are many similar studies in the literature, but in our study, the effects of external applied AdM over internal angiogenic factor alterations are striking. During obesity the expanding adipose tissue becomes hypoxic, (35) and both differentiation and hypoxia induce vascular endothelial growth factor (VEGF) expression by adipocytes (36,37). AdM injection increased VEGF levels thereby the vascularization of BAT which helps the energy expenditure in obese+AdM group, and on the other hand, AdM injection also increased VEGF levels of WAT in calorie restriction+AdM group. As a result, AdM regulates the vascularization of tissues (WAT or BAT) according to the individual's requirement. AdM may have a protective effect towards obesity, and according to metabolic situation of individual's adipose tissue, AdM application may provide consumption of energy by increasing vasculature of BAT in obese individuals. The system of organism itself and conventional methods for the combat of obesity together can be regulated again by organism. AdM specific binding sites are mostly found in lung tissue. AdM has a detractive role in pulmonary hypertension, causes pulmonary vasodilatation, and inhibits bronchoconstriction created by histamine and acetylcholine. AdM application increased AdM level in obese+AdM group than obese group.

Conclusion

The increased level of AdM in lung by AdM injection also suggests that the increased vascularization of lung supplies more oxygen which is required for energy expenditure with the vasodilatation effect of AdM, so burning of fat is facilitated. We think that further investigations must be made about the effect of angiogenic factors of obese individuals' not only in adipose tissues, but also in seemingly unrelated tissues as lung.

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The prevalence of celiac disease in healthy school children in Van City, east of Turkey: a screening study using a rapid test

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Abstract

Objective: Celiac disease is seen by increasing rates in the whole world. It may have a silent course besides having classical symptoms. It may result in serious complications if the diagnosis is delayed such as anemia, fatigue, vitamin K deficiency, excessive bruising and bleeding. The aim of this study is to detect celiac patients who have not been diagnosed yet in healthy school children.

Materials and Methods: Present study performed was in 1003 school children who are between 5-18 years old in Van city, east of Turkey. Celiac disease was investigated via rapid celiac testing (BiocardTM stick test).

Results: Percentages of the cases, 51.2% were female and 48.8% male. Test was positive in two (0.2%) patients. Ten (1%) patients had immunoglobulin A deficiency. In addition to these patients, one patient had been diagnosed as celiac disease beforehand.

Conclusion: The prevalence of celiac disease in Van city, east of Turkey in our study, shows a lower prevalence than in study which performed in our country previously

Keywords: Celiac disease, children, prevalence, rapid test

Introduction

As European Society for Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) defined, celiac disease (CD) is an immune-mediated systemic disorder elicited by gluten and related prolamines in genetically susceptible individuals and characterized by the presence of a variable combination of gluten-dependent clinical manifestations, CD-specific antibodies, HLA-DQ2 or HLA-DQ8 haplotypes, and enteropathy (1). CD is a permanent sensitivity to gluten, resulting in a disorder of inflammatory enteropathy with various degrees of severity, and a wide range of gastrointestinal and extraintestinal problems (2).

Different clinical classification of CD has been made: the typical, atypical, silent, potential, and latent. Today, the number of applicants with typical gastrointestinal symptoms is decreasing compared to atypical ones. The term “silent CD” is used for patients with positive serology, HLA-DQ2/DQ8 and histopathology, but without any suggestive clinic for CD. Latent CD has been defined for patients with HLA-DQ2/DQ8 positivity, without enteropathy, but had enteropathy for a particular time of the life either before or after. These patients may have or not positive CD antibody serology or symptoms and signs. The potential CD explains patients without histopathology despite the presence of positive CD antibody serology and HLA-DQ2/DQ8. These patients may or may not have symptoms and may or may not develop CD in the future. Today, patients with a diagnosis of CD are actually the tip of the iceberg above the water (2,3).

In our study, recognition of the patients remaining silent as well as determining CD prevalence in school-age children in Van city which is located at the eastern Turkey have been aimed by CD screening in school-age children considered to be healthy.

Material and Methods

Study group: The study was planned to be conducted on a total of 1000 patients among the school-age children in Van city aged between 5 and 18. Van City Directorate of National Education was applied to carry out the study in schools. Quick celiac tests were conducted at the designated schools by two doctors and two allied health personnel. Patients with positive test results were invited to pediatric gastroenterology clinic in our hospital and for conventional serum anti-tTG IgA antibody study and it was palled to confirm the diagnosis by duodenal biopsy.

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Description of Biocard testing

For CD screening study used a rapid and easy immunoglobulin A-class whole blood point-of-care test (Biocard™, Ani Biotech, Finland) which measure to immunoglobulin (Ig) A tissue transglutaminase (TTG) antibodies (anti-tTG) and total IgA according to instructions for use. One drop capillary blood, obtained by performing a finger prick with a sterile lancet, is mixed with the reagent solution in a capillary tube. Three drops of this mixture were applied to the test stick having two separate fields, test and control ones. Anti-tTG IgA antibodies bind to antigen in the test strip to form a visible line and provide results within 10 minutes. Two lines in both field indicate positive result for CD, one line in only control field negative result. If there is no line, IgA deficiency should be suspected.

Ethical approval and funding

Ethical permission was taken from Yuzuncu Yil University, Faculty of Medicine, Clinical Research Ethics Committee (Approval number: 05.12.2013/01). This work was supported by Research Fund of the Yuzuncu Yil University (Project Number: 2014-TF-B161).

Results

1003 patients including 51.2% female and 48.8% male were included in the study. The age and gender distribution of the children who participated in the study are presented in Table 1. According to test results, positivity for CD was detected in two children (0.2%). IgA deficiency was detected in ten (1%) patients. One patient was previously diagnosed with CD. The patients whose tests were verified positive did not apply to the hospital despite being invited for the test verification and if necessary for duodenal biopsy. If the patient pre-diagnosed with CD is included, test positivity was detected at the rate of 0.3%.

Table 1. Distribution of study group (n=1003) according their ages and genders.

Age Year	Gender		Rapid test positivity	IgA deficiency
	Girl	Boy		
5	31	38	-	-
6	76	76	-	1
7	123	126	1	1
8	85	100	-	3
9	46	40	1	1
14	34	18	-	-
15	17	29	-	1
16	44	26	1	2
17	43	30	-	1
18	15	6	-	-
Total	**514**	**489**	**3**	**10**

Discussion

The incidence and diagnosing of CD have increased with the development and widely use of serologic tests with high sensitivity and specificity. With serological screening tests, prevalence was determined as 1:105 in the United States, 1:100 in the UK, 1:77 in Sweden, 1:133 in Russia, 1:251 in Australia, 1:157 in Israel, 1:166 in Iran and 1:310 in India (4). In our country, in the study with the broad participation conducted in healthy school children, CD prevalence proved with biopsy was determined 1:212. On including the patients with high serological antibody titer positivity that cannot be biopsied and the previously diagnosed with CD, prevalence of CD has reached a value of 1:58 that indicates that it is fairly common in our country (5). CD is seen in all the world in varying rates but increasing incidences. In an earlier study conducted in our country, a small number of participation was from the province of Van city. In our study, we aimed to determine the prevalence in Van city. Test positivity for CD have been found at the rate of 0.2% in 1003 children. On including the previously diagnosed child, this value would be 0.3%. These values are considered as lower than expected. Both patients with test positivity did not come to the hospital in spite of being invited for performing verification and duodenal biopsy.

In our study, unlike previous studies in our country, rapid celiac test has been used instead the conventional method. Rapid celiac tests have been widely used in the world because of ease of application outside the hospital and getting quick results. However, there are studies indicating relatively low sensitivity. Serum anti-TTG IgA antibody studied by conventional method have a sensitivity of 96.4%, specificity of 97.7 (6). Biocard testing detects anti-TTG in capillary whole blood rapidly.

Mooney et al., in their study (7), investigated Biocard test and deaminated gliadin peptide antibodies (DGP)in 55 patients with positivity for endomysial antibody (EMA) and determined sensitivity 72.2% in Biocard test, and 94.4% in DGP test. Singh et al., in their study (8), conducted conventional anti-TTG and Biocard test with duodenal biopsy in 319 children suspected with CD , and determined sensitivity/specificity 93.8%/96.4% for conventional anti-TTG, and 83.6%/90% for Biocard test. Mooney et al., in another study (9) assessed Biocard rapid test, serum anti-TTG, EMA, and upper GI endoscopy with duodenal biopsies at the same visit in 523 patients had no prior diagnosis of CD, and 53 patients had known CD coming for reassessment. Sensitivity, specificity, positive predictive value, and negative predictive value of Biocard test were 70.1%, 96.6%, 85.4%, and 91.8%, respectively, sensitivity and specificity of TTG were 91.0% and 83.5%, respectively, and EMA were

83.8% and 97.5%, respectively. In comparison, they indicated that anti-TTG and EMA both performed significantly better than the rapid test, and proposed that the performance of rapid test was disappointing compared with standard serology and cannot at present be recommended within the context of an endoscopy unit. Korponay-Szabó et al. (10) scanned 2690 patients in primary care with rapid test. They found that rapid testing had a 78.1% sensitivity and 100% specificity for a final diagnosis of CD by biopsy, while sensitivity was 65.1% and specificity was 100% compared with combined results of IgA and IgG laboratory tests. According to these studies, it can be considered that rapid test has low sensitivity but high specificity.

Pichler et al., in their study (11), have applied Biocard test in 196 first and second degree relatives of CD patients and have found positivity in 3 patients. These 3 patients were later confirmed by serology and histology. Doğan et al., in their study (12), analyzed anti-TGG in 195 first-degree relatives of CD patients with conventional method, and detected a high level of positivity at the rate of 9.5%. Popp et al. (13) have detected positivity at the rate of 8% with Biocard test in first-degree relatives of CD patients. Oliveira et al. (14) detected Biocard test positivity at the rate of 4.5% in 268 first-degree relatives of children with CD, and diagnosed CD with histology at the rate of 2.6%.

Korkut et al. (15) have detected positivity in 2 of 100 patients with Biocard test in their study where they investigated prevalence of CD in adult patients fulfilling the Rome III criteria for irritable bowel syndrome. Kansu et al. (16) have investigated CD with Biocard test in 1047 children with abdominal pain-associated functional gastrointestinal system disorders, have found positivity in 13 patients and confirmed the diagnosis of CD in 10 of them.

Alarm et al. (17) have made a screening with a rapid test in Libyan Children, and have found positivity in 50 out of 2920 (1.7%). 20/50 have been confirmed by the ELISA determination. Biopsy-confirmed CD diagnosis was confirmed in 19 out of these 20. In addition, they found that serum ELISA anti-TTG IgA antibody was positive in 4 out of 800 rapid test negative children. CD prevalence was 0.79-1.13%. Karakoyun et al. (18) have found positivity in 4 out of 502 students of the department of nutrition and dietetics and medical school for CD screening with Biocard testing and confirmed the diagnosis with biopsy. IgA deficiency had not been detected on any of them. In our study, IgA deficiency was a ratio of 1%.

Coclusion

As a result, in our study, CD prevalence was found to be 0.3% in school-age children considered to be healthy (if the patient previously diagnosed with CD is included and if they were also proven by biopsy). This value is lower than expected. Biocard test's having a high specificity as seen in previous studies and low sensitivity is considered to contribute to this value being lower. The number of the test methods used for the diagnosis of CD is increasing. There is a need for the studies investigating the correlation of these methods with each other.

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Elastofibroma Dorsi: An Uncommon Soft Tissue Tumor

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Abstract

Elastofibroma dorsi is a rare clinical situation mostly encountered as a non-tender solid mass in inferior margin of scapula, typically in elder women. It is accepted as a pseudotumor.

55 year-old female patient complaining from a mass in her back, painful with shoulder movement is presented. The patient was referred with a suspicion of malignant tumor. Biopsy revealed that it was elastofibroma dorsi and also computerized tomography was used for detection of dimension and depth of the mass. After surgical removal, pathology of the specimen confirmed the biopsy. Differential diagnosis, clinical findings and pathophysiology is discussed.

During the follow-up seroma was realized 10 days after surgery and it was treated by 2 punctions performed in a week. No further surgical complications occurred in postoperative period and no recurrence was observed during one year follow up. Surgical removal is essential in symptomatic patients. Seroma is the most encountered complication especially if the tumor diameter is large. In some cases, biopsy may help to rule out malignancy.

Keywords: Elastofibroma, soft tissue, pseudotumor

Introduction

Elastofibroma dorsi (ED) is an uncommon, benign, pseudotumoral lesion, predominant in elderly women (1). The tumor is non-encapsulated, hypo cellular in nature, composed of elastic fibers, fat and collagen (2). The most common affected body part is infrascapular region. While most of the patients are asymptomatic besides a palpable mass, some patients are reported to have increased discomfort with shoulder movements. Differential diagnosis includes lipomas, fibro lipomas, hemangiomas and malignant tumors. Especially, large tumors which seem to be fixed by palpation, may require biopsy prior to surgical excision

Case

A 55-year-old woman was referred to our clinic for a mass in her left infrascapular region with a suspicion of malignant tumor. She realized it 3 years ago and stated progressive enlargement during the last 6 months. There was no resting pain; however she had discomfort with shoulder movements. There were no additional medical problems, and no familial malignancy in her history. Physical examination revealed a palpable, non-tender, fixed, solid mass at her left infrascapular region, which was approximately 10×15 cm.

Thorax computerized tomography (CT scan) revealed a heterogeneous, well circumscribed, non-encapsulated mass attached to the inferior border of scapula (Figure 1). Biopsy was taken under local anesthesia in order to rule out malignant tumor. Histologic examination revealed that it was elastofibroma.

The patient was operated under general anesthesia. The surgical approach included a 10 cm oblique incision parallel to intercostal line at left inferior scapular region. Latissimus dorsi muscle was transected to reach the mass. Rubber dense, 120×110 mm light colored mass was firmly attached to chest wall posteriorly between 6th and 9th costa, reaching the inferior border of scapula. Total excision, included the periost of costal bone where the tumor was fixed. Meticulous bleeding control was performed. Suction drain was applied for 3 days and firm dressing of the wound for 1 week in order to prevent hematoma. During the follow-up seroma was realized 10 days after surgery and it was treated by 2 punctions performed in a week. No further surgical complications occurred in post-operative period and no recurrence was observed during one- year follow up.

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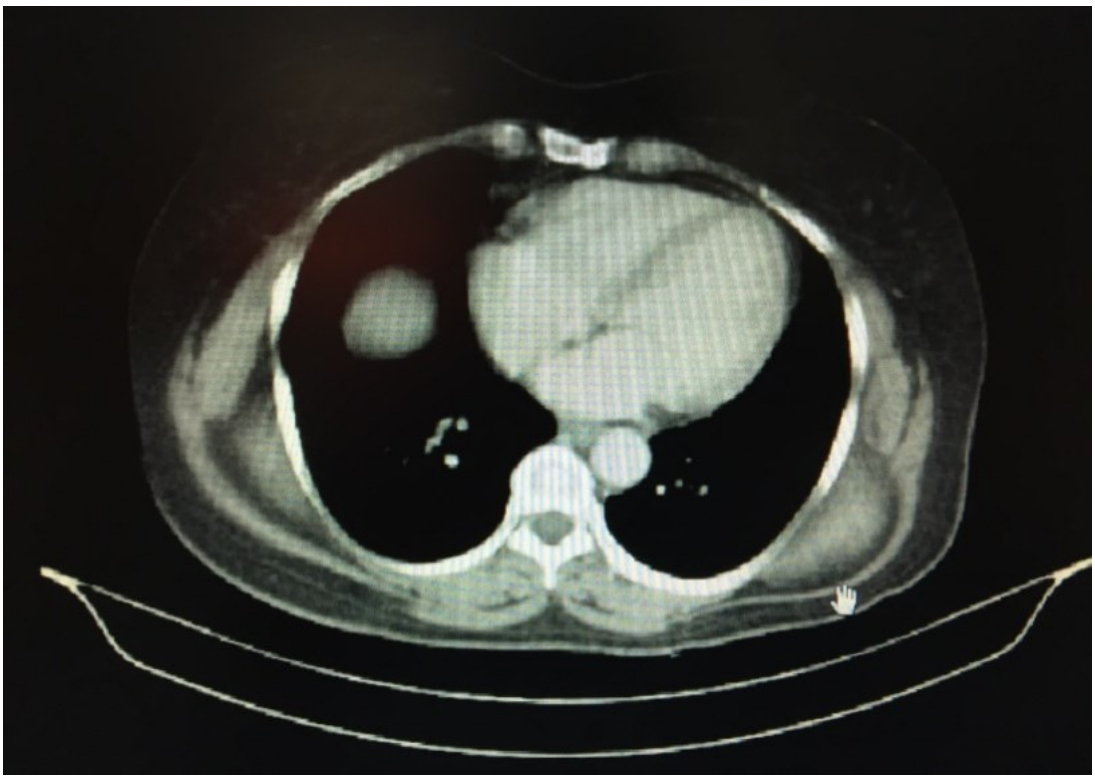

Figure 1: Thoracal CT image shows left infrascapular, well circumscribed mass, reaching chest wall.

Histologic examination of the lesion yielded a non-encapsulated excision material, circumscribed by adipose tissue and skeletal muscle streaks, rich in elastic fibers, finally diagnosed as elastofibroma consistent with prior biopsy

Discussion

Elastofibroma dorsi is a rare clinical entity which is typically seen in sixth decade of life predominantly in female patients (3). Usually it is asymptomatic and unilateral (4). However, bilateral and painful cases are also presented in the literature (5,6). Typical location is the inferior border of right scapula. Other rare locations are, forefoot, hand, breast, stomach and mediastinum (7,8). Our patient seems to carry some important characteristic properties of this clinical situation. She was 55-years-old, had a unilateral mass on her infrascapular border and it was only painful with shoulder movements. However, it was a fixed and solid lesion and the patient stated rapid growth during the last 6 months. Therefore we preferred to rule out malignancy prior to final surgery.

There are several scenarios to explain the pathogenesis of ED. Minor micro traumas due to friction between the inferior border of scapula and chest wall may cause reactive fibromatosis (9). Hypoperfusion by the enlargement of the lesion, enzyme deficiency, elastotic degeneration have also been discussed for pathogenesis (10,11).

There is a theory suggesting that the tumor arises from chest wall periosteum (12). In our case the tumor was fixed to periosteum and we had to remove it with the tumor. Another point is familial inheritance; a genetic instability in 1st chromosome has been shown to be linked with ED (13). In our case there was no family history.

Diagnostic approaches are not specific and physical examination, combined with an imaging modality such as CT or MRI would be enough. Some authors recommend fine needle aspiration biopsy, however hypo cellular nature of the lesion decreases the chance to obtain successful results (14). Therefore we preferred incisional biopsy to rule out malignancy.

In symptomatic cases, surgical excision is the recommended and sufficient treatment modality (15). Most encountered complications are seroma, hematoma and infection (16). Seroma was also detected in our case, 10 days post-operatively, resolved in a week by two punctions and drainage.

Elastofibroma dorsi should be kept in mind especially in middle-aged female patients presenting with fixed infrascapular mass. Surgical treatment is sufficient in symptomatic cases; biopsy would be useful if there is a suspicion of malignancy.

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An unusual cause of delayed full enteral feeding and prolonged hospital stay in a newborn with gastroschisis: Congenital Hypothyroidism

Sevgi Buyukbese Sarsu[1*]

Abstract

Gastroschisis, is a prevalently encountered congenital disease of the newborns where intraabdominal organs protrude through a full-thickness defect in the anterior abdominal wall without an overlying sac. In recent years, an increase in the global incidence of gastroschisis has been reported. Although its etiology is not known fully, it is usually associated with young maternal age. Delay in the transition to full-calorie enteral feeding (ENT) in a newborn with gastroschisis is a result of bowel dysfunction which is a major morbidity developing due to exposure of bowels to amniotic fluid. Consequently, newborn may require long-term TPN treatment, and sepsis may onset secondary to prolonged mechanical ventilation, and TPN treatment, and infection,.

Global incidence of congenital hypothyroidism (CH) in live births is 1:3000-4000. Widely encountered symptoms may include prolonged jaundice, constipation, distended abdomen, and poor feeding. The diagnosis should be confirmed by finding an elevated serum TSH and low T4 or free T4 level. In the literature, transient hypothyroidism has been reported in cases who underwent only silo operation, and povidone iodine dressings,. Association of hypothyroidism with delayed transition to full enteral feeding, and prolonged hospital stay in gastroschisis has not been reported previously. In newborns with gastroschisis who underwent primary facial repair, thyroid functions should be controlled at appropriate times, and followed up closely.

Keywords: Gastroschisis, Enteral nutrition, Length of Stay, Congenital, Hypothyroidism, Newborn

Introduction

The term gastroschisis which is also named as abdominoschisis, laparoschisis, and paraomphalocele is derived from ancient Greek words for belly (gaster), and fissure (schisis). It is an anterior abdominal wall defect which is mostly localized on the right side with an incidence of 1 of 4000 births ve 4.4/10000 in live births (1-3). The defect is not covered by a sac and the rectus muscles meet in the midline at the xiphoid. This is an embryological developmental defect with male predominance (4). The etiology of gastroschisis is unknown but there is an association with young maternal age. There are two theories regarding the formation of gastroschisis. One theory suggests that involution of the right umbilical vein causes necrosis in the abdominal wall when physiological umbilical hernia is formed, leading to a right-sided defect. The second theory states that the right omphalomesenteric or vitelline artery prematurely involutes causing a weakening in the abdominal wall through which the intestinal contents protrudes out (3,5). The organs are not enclosed in membranes; hence they are floating in the amniotic fluid resulting in perivisceritis, perivisceral adhesions, pseudomembranous covering, short mesentry, poor peristalsis and significant nutrient absorption imbalance (3).

Patients with gastroschisis can be divided into two groups as simple and complex gastroschisis (6). In complex gastroschisis, gastrointestinal anomalies such as intestinal atresia, stenosis, perforation, or volvulus may be seen. Simple gastroschisis is repaired by primary fascial closure and preformed silo while complex gastroschisis. In a recent UK study average hospitalization periods for simple, and complex gastroschisis have been reported as 24 days, and 47 days, respectively (6). Prolonged postoperative hospital stay in a patient with gastroschisis stem from complications as necrotizing enterocolitis, feeding difficulties and cholestatic jaundice, wound evisceration, wound infection, pneumonia and septicemia.

Congenital Hypothyroidism (CH) is one of the most common preventable causes of mental retardation. Its worldwide incidence is 1:3000-4000 live births. Ideally universal screening at 3-4 days of age should be done so as to detect CH. It accompanies mostly cardiac malformations, but comorbidities as neurologic abnormalities, cleft palate, and genitourinary malformation can be also seen. Increased incidence of hypothyroidism has been also reported among patients with Down syndrome.

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Herein we report on CH as an unusual cause of delayed transition into full enteral feeding, and prolonged hospital stay in a newborn with gastroschisis

Case

A 15-year-old Syrian refugee mother (G1, P1) gave birth to a male newborn with gastroschisis (weight,2100 g; p 90. ; length, 43 cm , p 50, and head circumference, 31 cm, p75) via spontaneous vaginal delivery at 32nd gestational week in the Cengiz Gokcek Obstetrics and Children's Hospital who was then brought into male neonatal surgical care. His mother did not have any diseases during her pregnancy, and since she had not been followed up during antenatal period, she hadn't undergone ultra-sonographic and serologic tests, and eventually her gastroschisis was not diagnosed till delivery.

Physical examination showed a large gastroschisis defect on the anterior abdominal wall to the right of an intact umbilical cord, without traces of membrane with an exteriorization of dilated bowel loops with swollen and thickened walls. Umbilical cord examination confirmed the presence of a single umbilical artery. All of the herniated contents were wrapped in moist and warm sterile dressings, umbilical venous catheterization was applied for fluid replacement, and antibiotic prophylaxis (ampicillin and gentamicin) was administered (Figure 1).

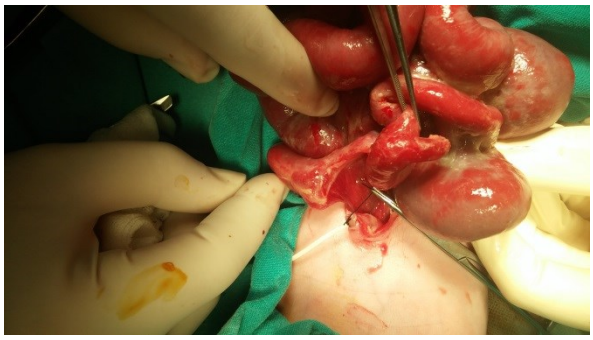

Figure 1. Umbilical vein catheterization for fluid replacement and antibiotic prophylaxis during preoperative period.

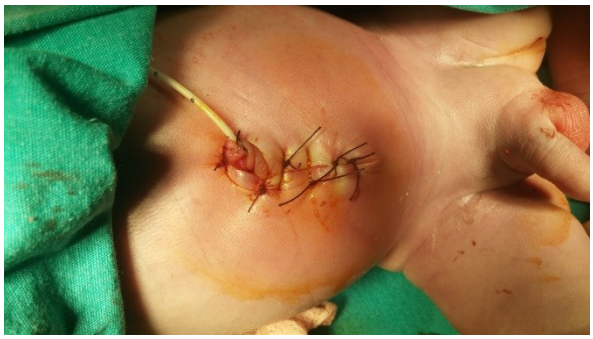

Figure 2. Primary repair of gastroschisis.

Surgical procedures were performed under general anesthesia after tracheal intubation, and prevention of hypothermia. Incision was extended vertically on either side for 2 cm. Intestinal tract was not atretic. There were no other abnormalities in the newborn. Abdominal wall defect was primarily closed without the need for silo reduction (Figure 2). Although on routine screening test TSH value was detected as 70 µIU/ml, since the test was performed within the first 24 hours of life this result was deemed to be false positive

The patient was kept on mechanical ventilation for 2 days. Total parenteral nutrition started. Enteral nutrition was started at 6 days of life but could not be progressively increased in amount. He was receiving orally only breast milk, and after three feedings he vomited once (non-bilious vomitus) after every three feeds, and defecated scarce amount stool once a day. Besides, abdominal distension was detected on 15th day of his life, she was consulted to pediatric endocrinology, and levothyroxine therapy was initiated when higher levels of free T3 [2.10 (2.3-5.0) pg/ml], free T4 [0.67 (0.80-2.0) ng/dl], and TSH [150 (0.72-11) µIU/ml] were detected. Thyroid US was unremarkable. After treatment, the patient could tolerate full enteral feeding, so he was discharged on postoperative 20th day without complication

Written informed consent was obtained from the patient's legal guardian(s) for the publication of this case report. The study was approved by the local ethics committee (Conclusion no:19.11.2015/27).

Discussion

Gastroschisis is a neonatal disease with a gradually increasing incidence (7). Although its pathogenesis is not known precisely yet, gynecological immaturity and poor nutritional status have been associated with this neonatal congenital (8). Our case was a 15-year-old Syrian refugee. Delay in the transition to full enteral feeding because of intestinal dysfunction in newborns with gastroschisis is a major neonatal morbidity. It results in prolonged hospital stay, and longer administration of TPN, development of sepsis, and infection. In previous studies, shorter duration of TPN, and hospital stay, lower rates of infectious complications, and more favorable prognosis have been reported in newborns whose enteral feeding was initiated at an early stage. (9).

Enteral feeds are usually initiated at a low volume and its volume is gradually increased if tolerated. Our case gradually started to receive breast milk. Progressive increase in the frequency, and amount of breast feeding could not be achieved, Due to newborn's intolerance to milk Clinical criteria for initiation of enteral feeding in cases with gastroschisis include definitive closure of the defect, detection of nonbilious nasogastric drainage fluid, maintenance of regular

defecation pattern, and absence of abdominal distension (9). In consideration of these criteria, enteral feeding was initiated on 6. day of newborn's life. In newborns who started to receive enteral feeds within the first 7 days of their lives length of hospitalization, and days on TPN decreased, and infectious complications as fever were less frequently encountered when compared with patients whose enteral feeds were initiated 21 days after closure of the abdominal defect (9). Bucher et. al. found that time to closure was associated with earlier age of full enteric feeding and decreased TPN duration (10). Cases that underwent primary closure start to receive enteral feeding earlier than those treated with silo reduction procedure. In a 2013 study, Baud et al. showed that outcomes were improved for those who started to receive oral enteral nutrition before 37 weeks, and incidence of intestinal atresia, necrosis or perforation also decreased (11). Prolonged exposure to amniotic fluid may damage intestinal wall. Our case with gastroschisis was delivered spontaneously at 32. gestational week via vaginal route. However in another study, any difference in transition to enteral feeding was not detected between newborns delivered before or after 37. gestational week. (12).

A newborn with gastroschisis should be immediately referred to surgery for the repair of abdominal wall defect. Primary fascial closure of the abdominal wall defect has outcomes superior to silo reduction procedure, and it should be considered in all newborns with gastroschisis without increased intraabdominal pressure, and suitable abdominal anatomy (13). Our case was suitable for primary fascial closure. Studies of gastroschisis typically focus on the surgical complications which may develop in a newborn with gastroschisis include necrotizing enterocolitis, feeding difficulties, and cholestatic jaundice, wound evisceration, and infection, pneumonia , and septicemia (14-16). Besides, in 26.7% of the cases with gastroschisis developmental delay was detected based on BSID III criteria (17). In the same study it was reported that all cases with developmental delay, and transient hypothyroidism had received povidone iodine (PVP-I) dressings, and undergone silo operations before Transient hypothyroidism may be caused by maternal or neonatal factors. Maternal factors include anti-thyroid medications, trans placental thyrotropin receptor blocking antibodies and iodine deficiency or excess. Our case had not maternal factors. Neonatal factors include, neonatal iodine deficiency or excess, congenital liver hemangiomas and mutations in the genes encoding for DUOX and DUOXA2. We didn't perform genetic tests in our case. Transient neonatal hypothyroidism may develop secondary to giant omphalocele which is a prevalent anterior wall defect, escharification of omphalocele sac, long-term use of PVP-I for escharification, and epithelialization of omphalocele, and hyper-permeability of neonatal tissues. Topical PVP-I can rarely induce this condition. In this case if omphalocele sac atrofies, then iodine exerts minimal systemic effects, and since transient thyroid dysfunction develops, thyroid supplementation is not required Delay in transition to full enteral feeding, and prolonged hospital stay in association with CH have not been reported in cases with gastroschisis before.

Signs and symptoms of hypothyroidism include postmaturity, macrosomia or wide open posterior fontanel at birth or abdominal distension, constipation, poor feeding, prolonged jaundice, hypotonia, hoarse cry, umbilical hernia, macroglossia, or dry edematous skin in infancy. In our case the first three clinical symptoms were detected. In the absence of newborn screening programs, the diagnosis of CH is made after development of clinical manifestations. Thyroid function tests should be performed on all newborns. In our hospital routine screening tests are being performed.. The time at which the sample is taken may vary between centers, with the majority taking blood from a heel prick at 24 hours of age to minimize the false- positive higher TSH measurement due to the physiological neonatal TSH surge that elevates TSH levels and causes dynamic T4 and T3 changes in the first 1 or 2 days after birth. Early discharge of mothers after delivery has increased the ratio of false- positive TSH elevations. If this is not possible, testing should be performed before discharge or within seven days of birth. False-positive TSH elevations may be found in specimens collected at 24 to 48 hours after birth, and false-negative results may be also seen. However in this case blood samples of this newborn were drawn to screen TSH , and T4 levels within the first 24 hours of his life, and increased TSH level was thought to be a false-positive result, and so overlooked. A minority of patients develop CH as a result of a hereditary defect in thyroid hormone biosynthesis. As was the case with our patient, this condition progresses with low T4 and elevated TSH levels. In this case levothyroxine (L-thyroxine) should be initiated at daily doses of 10- 15 µg/kg as soon as the diagnosis was made. The l-thyroxine tablet should be crushed, mixed with breast milk, formula or water and fed to the infant. Regular monitoring should be performed.

Conclusion

Delay in the transition to full enteral feeding , and prolonged hospital stay in a newborn who underwent primary repair for gastroschisis may be due to CH. Even if silo operation is not performed, screening tests for CH should be performed between 2th, and 4th Post-natal days, and the patient should be closely followed-up.

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Successful treatment of severe aplastic anemia with eltrombopag

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Abstract

Aplastic anemia is a clinical syndrome characterized by peripheral pancytopenia and deficiency of hematopoietic precursors in the bone marrow. Allogeneic hematopoietic stem cell transplantation (AHSCT) should be considered as first line treatment for young patients with an available donor. However, alternative therapy options are scant in patients who are not candidates for transplantation. Here, we report the efficacy of eltrombopag in a case of severe aplastic anemia. Case Presentation: Twenty-two years old female patient was admitted to the Marmara University Hospital because of severe aplastic anemia. There was not an available HLA-matched sibling donor and immunosuppressive treatment with horse-derived ATG (40 mg per day for 5 days) and cyclosporine (5 mg/kg per day) was started. At the sixth month of therapy she was still in need of transfusion. Eltrombopag was prescribed at a dose of 50 mg and the dose was increased up to 150 mg per day in 2 months. Successful response was noted within 2 weeks of 150 mg dosage and this response was sustained at the 4th month following discontinuation of drug. Conclusion: Eltrombopag provides good and permanent clinical response in refractory severe aplastic anemia.

Key words: Eltrombopag, Aplastic anemia

Introduction

Aplastic anemia is an autoimmune disease of the bone marrow characterized by deficiency of hematopoietic precursors and peripheral pancytopenia (1). It was suggested that activated cytotoxic T cells expressing inhibitory cytokines like Interferon- γ and Tumor Necrosis Factor- α (TNF α), take role in the immune destruction of hematopoietic stem cells (2). The standard treatment of patients who are ineligible for transplantation consists of immunosuppressive treatment with ATG and cyclosporine. Hematologic response is achieved in about two thirds of the patients with this treatment. However, AHSCT is recommended for those bellow age 40, if HLA-matched sibling is available.

During the course of aplastic anemia, infections following neutropenia may lead to death or fatal hemorrhages can occur because of thrombocytopenia (4). Although immunosuppressive treatment improves the outcomes, pancytopenia persists in about 30 % of patients after ATG and cyclosporine (3,5,6). AHSCT is an option where donor is available; however there is high risk of infections, graft versus host disease (GvHD) and graft failure (5). Treatment options other than AHSCT are limited with growth factors, supportive care and androgens (6).

Salvage treatment with immunosuppressive drugs may be effective in some patients, but intensification with rabbit-derived ATG, sirolimus or mycophenolate mofetil does not improve response rates (7,8).

Thrombopoietin is the main regulator of thrombocyte production via c-MPL receptor in megakaryocytes. Activation of the pathway results in maturation and release of thrombocytes (9). Stimulation of c-MPL signal may overcome the decrease in hematopoietic stem cells in aplastic anemia. Eltrombopag is an oral Thrombopoietin receptor agonist, which binds c-MPL ligand and enhances release of thrombocytes from mature megakaryocytes. It was approved by FDA (US Food and Drug Administration) for treatment of chronic ITP (10). The critical role of thrombopoietin in the growth and differentiation of hematopoietic stem cell is demonstrated in a form of congenital bone marrow failure due to c-MPL deficiency (11). Regarding this observation, a prospective phase 2 study was designed to evaluate the efficacy of eltrombopag in aplastic anemia and it was shown to be effective in patients non-responsive to immunosuppressive agents.

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In this study, the normalization of all three lines in the bone marrow was observed and in 44% of patients hematologic response was achieved in at least one line (12).

In this case, we aimed to report our successful results with eltrombopag in a transplant ineligible patient who is unresponsive to immunosuppressive drugs.

Case

Twenty-two years old female patient was admitted to the emergency unit of Marmara University Hospital in September 2013, because of ecchymosis on the arm and bleeding gums. She also had menorrhagia. These complaints existed for the last one-week. Her physical examination was normal. Laboratory tests revealed pancytopenia and slightly increased transaminases (AST:54, ALT:85).

Other biochemical tests were in normal ranges. Her blood group was A Rh negative. The patient was hospitalized at our hematology clinic. Peripheral blood smear examination showed 16 bands, 14 neutrophils, 69 lymphocytes, anisochromia, anisocytosis and microcytosis and average number of thrombocytes in each field was 1-2.

There was no atypical cell. Direct and indirect coombs were negative. Erythrocyte sedimentation rate was normal. PNH clone was negative. Bone marrow biopsy showed severe hypocellularity. Considering bone marrow biopsy and pancytopenia on the peripheral blood, the diagnosis of severe aplastic was established.

HLA typing was done for the patient and her siblings, however a HLA-matched sibling donor was not available. Horse-derived ATG (ATGAM) (40 mg per day for 5 days) and cyclosporine (5 mg/kg per day) was given starting at day 12.11.2013. The documentation of blood count follow-up after immunosuppressive therapy is shown in the figure 1.

At the sixth month of therapy with ATGAM and cyclosporine, there was not enough response, transfusion requirement was continuing and cyclosporine related side effects like hirsutism and gum hypertrophy were emerging. After taking the required permissions from the government, eltrombopag was prescribed at a dose of 50 mg per day. Blood count was controlled every 2 weeks and the dose was increased by 25 mg. There was no response at the doses of 50, 75 and 100 mg per day. However, 2 weeks after practicing 150 mg per day, there was increase in the number of neutrophils and thrombocytes. Response assessment was done by bone marrow biopsy, which was taken at the end of the first month with eltrombopag. The cellularity was increased to 50 % and the maturation of all three series was normal. During the follow-up, after the dose was increased to 150 mg per day, cytopenias have begun resolving. However, the dose was decreased to 75 mg per day when the thrombocyte number was 154 000. Two weeks later, the dose was decreased to 50 mg and then to 25 mg per day. Later then, the treatment was terminated since the blood count was in normal range. Eltrombopag did not cause any increase in transaminases during the therapy and the response was preserved at the 4th month of discontinuation.

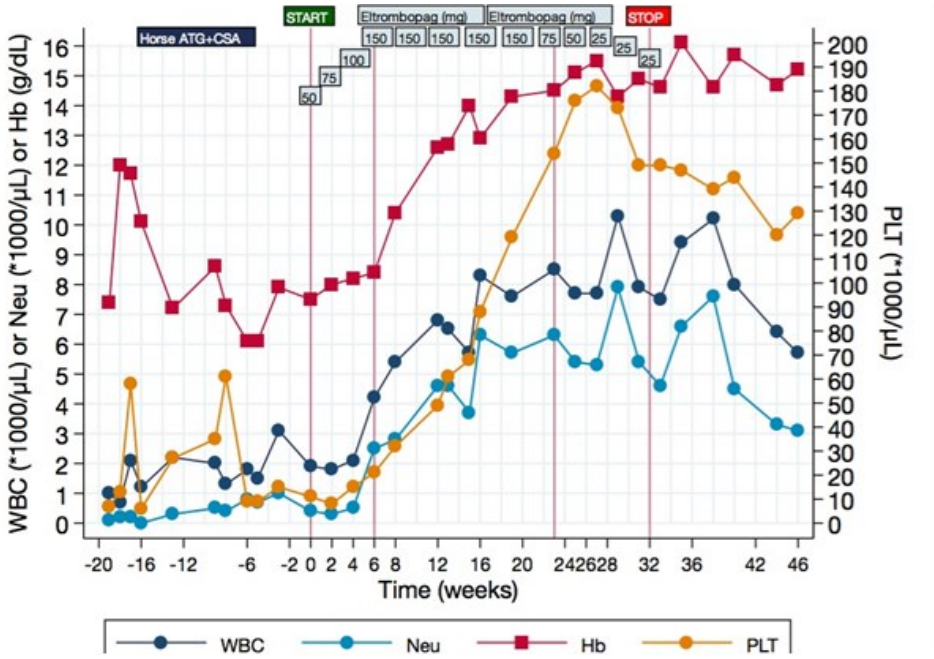

Figure 1: Progress of blood counts during follow-up

Discussion

It is thought that severe aplastic anemia develops after an autoimmune attack to the bone marrow, which results in paucity of hematopoietic stem cells and progenitor cells (7). Standard treatment of the disease is immunosuppressive therapy with ATG and cyclosporine. With this treatment, hematologic response is achieved in two thirds of the patients (3). However, allogeneic hematopoietic stem cell transplantation (AHSCT) is recommended for those younger than 40 years, if there is an available donor (4).

Most of the patients are in need of repeated transfusions which may result in hemosiderosis, alloimmunization or transfusion related infections. Therefore, novel therapies are required for patients who are not candidates for AHSCT and unresponsive to immunosuppressive agents. Eltrombopag is a low molecular weight synthetic agonist of thrombopoietin receptor and it may improve hematopoiesis by stimulating c-MPL receptor in refractory aplastic anemia.

Olnes et al. reported clinical improvement of thrombocytes, erythrocytes and neutrophils in 11 of 25 patients who used eltrombopag continuously. Moreover, they detected normalization of cellularity in all 3 series of bone marrow (12). Similarly, Desmond et al. observed decreased transfusion need and significantly increased blood counts in 40% of patients with severe aplastic anemia resistant to immunosuppressive drugs. In this study, they determined hematologic recovery in at least one serial among 17 (40%) of 43 patients, while recovery in all 3 series determined in 7 (16.3%). In addition, at the 12th month after discontinuation of eltrombopag, cellularity of the bone marrow was still normal in 5 patients (13).

The disease relapse is expected after discontinuation of eltrombopag in patients with ITP (14). However, continuous treatment may not be necessary in severe aplastic anemia in order to maintain permanently sufficient hematopoiesis. Eltrombopag may have different mechanisms of action in these two diseases. In ITP, the stimulation of megakaryocytes with eltrombopag is greater than physiologic stimulus (13). As indicated previously, the direct stimulation of stem cells restores the number of hematopoietic cells in severe aplastic anemia (13).

The required dosage of drug in ITP is lower than the doses required in severe aplastic anemia. In the study by Desmond the lowest dose for response is 100 mg (13). Similarly, our patient did not respond to treatment with doses 50, 75 and 100 mg respectively. Then, the use of 150 mg per day resulted in improvement in all 3 series within 4 weeks. The complete response was sustained at 4 months after discontinuation of eltrombopag.

Similar to the presented literature above, in our patient we also have experienced successful results with eltrombopag. However, it should be kept in mind that there was only 6 weeks between the cessation of cyclosporine and the beginning of eltrombopag and we cannot clearly rule out the possibility of a late response by immunosuppressive treatment.

In addition, severe aplastic anemia bears a risk of clonal bone marrow dysfunction like cytogenetic abnormality and leukemic transformation. Although, there is no clear evidence of an increased clonal transformation with eltrombopag, in a large observational study, 15% of patients were reported to have risk of clonal transformation (15). So, there is need for more controlled studies.

In conclusion, eltrombopag provides good clinical responses in refractory severe aplastic anemia and may be used in patients who don't have any other treatment option. Since, it is possible to gain permanent response, the treatment should be discontinued with close follow-up after sufficient clinical response is obtained.

Conflict of Interest: The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Vesicoperitoneal fistula: A rare late complication of laparoscopic removal of intrauterine device

Oktay Ucer[1*], Mehmet Bilgehan Yuksel[1], Gokhan Temeltas[1], Talha Muezzinoglu[1]

Abstract

We present a case of vesicoperitoneal fistula occurring 12 years after laparoscopic removal of the intrauterine device.

A 30-year-old primiparous woman presented with acute abdominal pain. On examination, there were sensitivity and painful of all the abdomen quadrants on gentle palpation. The diagnostic workup included transabdominal ultrasonography and contrast computed tomography that revealed leakage of contrast into the peritoneal cavity from the bladder. At laparotomy, the fistula tract was excised.

Vesicoperitoneal fistula is a rare major complication of laparoscopic surgeries and occurs in early postoperative period. We observed the vesicoperitoneal fistula as a late complication of laparoscopic approach in the present case. This may be due to the thinning of a urachal diverticulum wall in the bladder during the laparoscopic procedure.

Keywords: Complication, Laparoscopy, Vesicoperitoneal fistula.

Introduction

A vesicoperitoneal fistula is an epithelialized communication between the bladder and peritoneal cavity. It is an extremely rare condition and occurs as an early complication of obstetric or gynaecological interventions (1). We present a case of vesicoperitoneal fistula as a late complication of laparoscopy that occurred 12 years after laparoscopic removal of the intrauterine device

Case

A 30-year-old primiparous woman was presented to the department of emergency service at our hospital with acute abdominal pain. The surgery history of the patient was only the presence of a laparoscopic removal of the intrauterine device 12 years ago. She had no any history of recurrent paint, recurrent urinary tract infection, and gastrointestinal discomfort. Abdominal ultrasonography and computed tomography revealed intra-abdominal free fluid collection and no evidence of intra-abdominal organ injury.

She was referred to our clinic with the suspicion of bladder perforation. On examination, there were sensitivity and painful of all the abdomen quadrants on gentle palpation. Computed tomographic cystography demonstrated a leakage of contrast into the peritoneal cavity from posterosuperior wall of the bladder (Figure 1A).

A foley catheter was inserted into the bladder of the patient and she was hospitalized in our clinic. At laparotomy, the vesicoperitoneal fistula tract was excised, and peritoneum and bladder were sutured separately. The median umbilical ligament was intact. The beginning of the fistula tract was just below the location that the entry into the bladder of this ligament. The postoperative period of the patient was uneventful. The patient was examined 2 weeks after the procedure. Postoperative cystography revealed none leakage of contrast into the peritoneal area (Figure 1B). So, the foley catheter was removed. There has been no sign of fistula and the patient remains asymptomatic for 3 months. The patient provided written consent to use the information for the case report.

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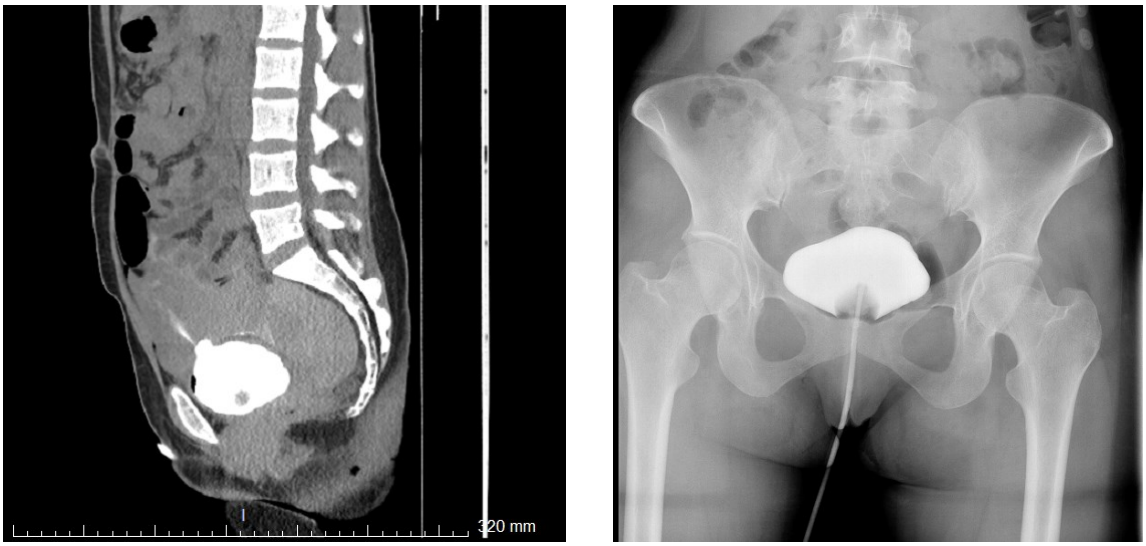

Figure 1. A: The leakage of contrast into the peritoneal area from the bladder in the preoperative computed tomographic cystography. B: The view of the bladder in the cystography two weeks after the operation.

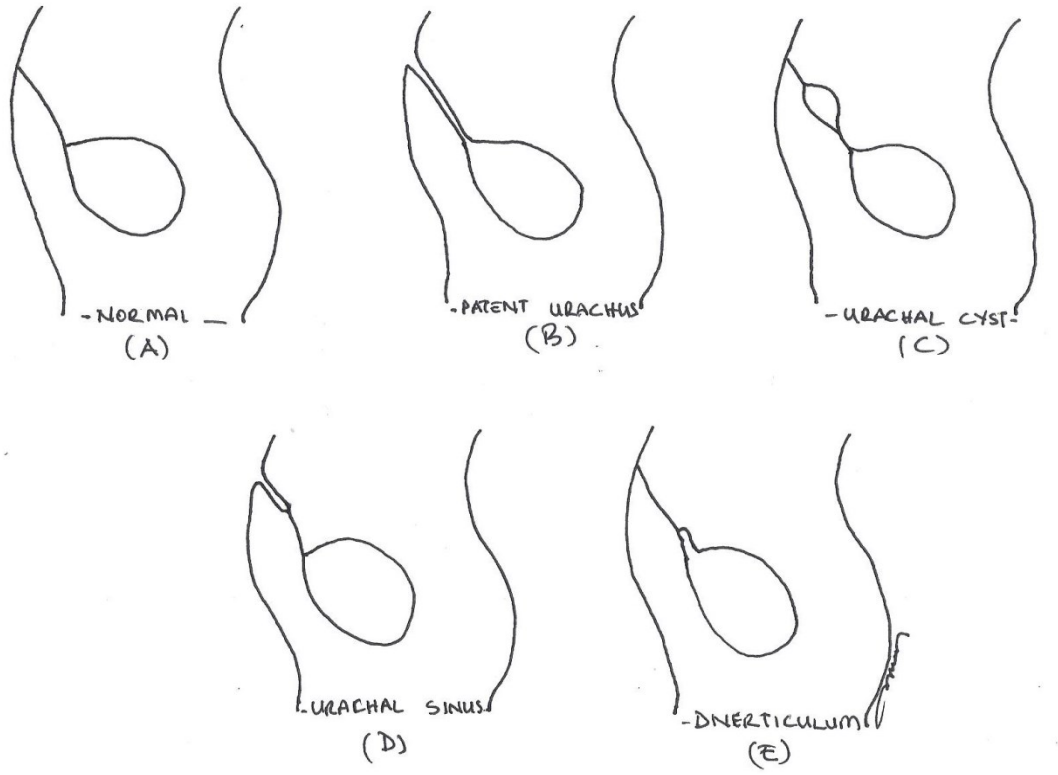

Figure 2. Urachal abnormalities (A: Normal, B: Patent urachus, C: Urachal cyst, D: Urachal sinus, E: Urachal diverticulum)

Discussion

Laparoscopy is now widely recognized as an indispensable tool in gynaecologic surgery. The incidence of vesicovaginal fistula after laparoscopic hysterectomy is approximately 1 in 455(2,3). Whereas, rates of vesicoperitoneal fistula after laparoscopic surgery remain unclear. Donnez et al (3) observed only one vesicoperitoneal fistula in their series of 3190 laparoscopic hysterectomies (0,06%). The vesicoperitoneal fistula was diagnosed 6 days after surgery. The patient presented with acute pelvic pain and ultrasound revealed the presence of liquid in the peritoneal area. The diagnosis of the fistula was made by computed tomography scan. A Foley catheter was left in place for 14 days. Only two patients with vesicoperitoneal fistulas reported in the literature to date. The traumatic vesicoperitoneal fistula presented within days with acute onset abdominal pain following emergency caesarean section. Although iatrogenic bladder injury may have occurred in this case, it remains a matter of speculation (4). The other case presented with chronical abdominal pain one year after an emergency caesarean section for fetal bradycardia (5).

Vesicoperitoneal fistula is a rare major complication of laparoscopic surgeries and occurs in early postoperative period. To our best knowledge, this is first case of vesicoperitoneal fistula that occurred a long time (12 years) after a laparoscopic surgery in literature to date. In the medical history of the patient, there were no surgeries or diseases except the removal of intrauterine device. The beginning of the fistula was at posterosuperior of the bladder and just below the median umbilical ligament. We think that the vesicoperitoneal fistula might be due to the thinning of a urachal diverticulum wall (Figure 2) in the bladder during the umbilical port insertion in the laparoscopic procedure.

Conclusion

Vesicoperitoneal fistula may be rarely experienced as a late postoperative complication of laparoscopic surgery. We should consider this issue in patients with acute abdominal pain and a history of laparoscopic surgery

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Extrude sequestrum spontaneous regression of lumbar disc hernia: case report

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Abstract

The correct approach to the lumbar disc hernia is subject to debate. Although a rare case of lumbar disc herniation with spontaneous regression, to be seen and is a well-known phenomenon commonly reported. But the underlying mechanism has not been fully clarified. Proposed mechanisms are enzymatic degradation and phagocytosis, dehydration and the retraction of a herniated disc in the annulus fibrosus. Cauda equina syndrome, despite the progressive narcotic pain goes outside and progressive neurological deficits, conservative treatment should be given priority to patients. Think about the possibility that spontaneously regressed with medical treatment and follow-up of disc herniation, should not rush to surgery. In our case, the level of lumbar disc herniation was presented on spontaneously regressed patients. The patient's clinical condition is improved in accordance with the resolution of the disc herniation and this is confirmed by magnetic resonance imaging.

Key words: Disc herniation, Sequestration, Spontaneous Regression

Introduction

Radicular ache was defined for the first time by Dandy due to extradural mass in 1929 (1). Mixter and Barr defined the way that extrude disc causes sciatica pain and the surgical approach to the problem in 1934 (2). Teplick and Haksin published the first paper by using spontaneous regression in lumbar disc hernia, using MRI. With the proliferation of MRI in clinic use and its increased accessibility, the spontaneous regression in lumbar disc hernia has been increasingly reported (3). The most important factor that affects the result and the success of disc surgery is the selection of the patient (4).

The minimal invasive methods that are developed in recent years are increasing the number of patients who have surgical operation. Therefore, the selection of the patient to go under surgery is very important. In this essay, a patient with radiculopathy whose symptoms were fully refined with the resolution of extrude-sequestrum disc part which caused radicular pain with a level of L4-5.

Case

Forty nine years old male patient, has applied to our polyclinic in June, 2013, with a complain of a left leg pain, a pricking and tingle starting from his left calf and going down to his ankles, in the inspection, There was 25 degrees positive laseque on the left leg, no motor deficit, L4-5 left dermatomal hypoesthesia and left achilles hypoactive reflex was found.

In the lumbar MRI inspection, in both sagittal sections (pic-1a) and axial sections (pic-1b) left L4-L5 sequestrum disc hernia was detected. With the present symptoms, the patient was recommended to have an operation.

However, the patient did not accept having an operation. As a medical treatment, methylprednisolone acetate 40 milligrams; intramuscular three days intermittently 3 units in total, asemetacin 90 grams capsule; 1 in a day, chlorzoxazone 250 milligrams + a tablet which includes 300 milligrams of paracetamol ; 3 in every day started.

In the follow-ups, the pain complaints and radicular symptoms were mended but hypoesthesia continued. In terms of hypoesthesia, the patient was given 150 milligrams of pregabalin capsule, two times in a day. Spontaneous regression on the sagittal (pic-1a) and axial (pic-1b) left L4-L5 sequestrum disc hernia were observed in the lumber MRI inspection of the patient in March, 2014,

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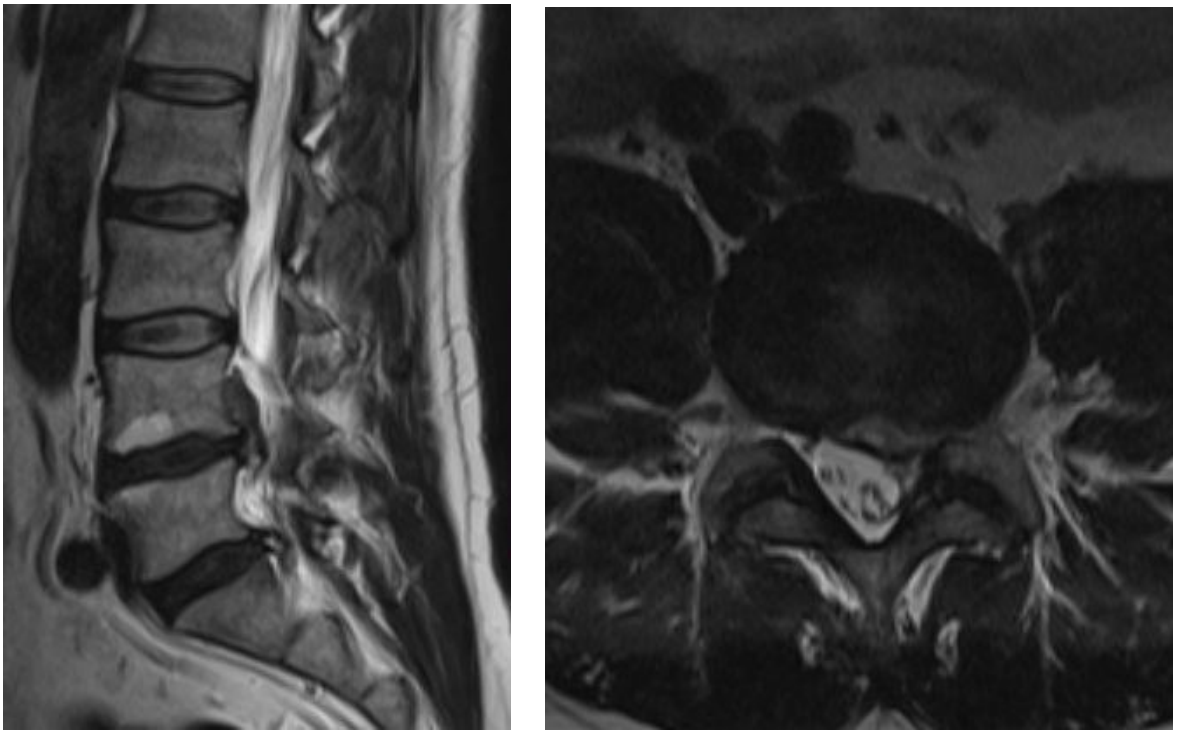

Figure 1. A) Disc in T2 weighted sagittal in MRI inspection, L5 level sequestrum herni is seen.
B) Sequestrum in T2 weighted axial MRI inspection, left L4-L5 L4 herni is seen.

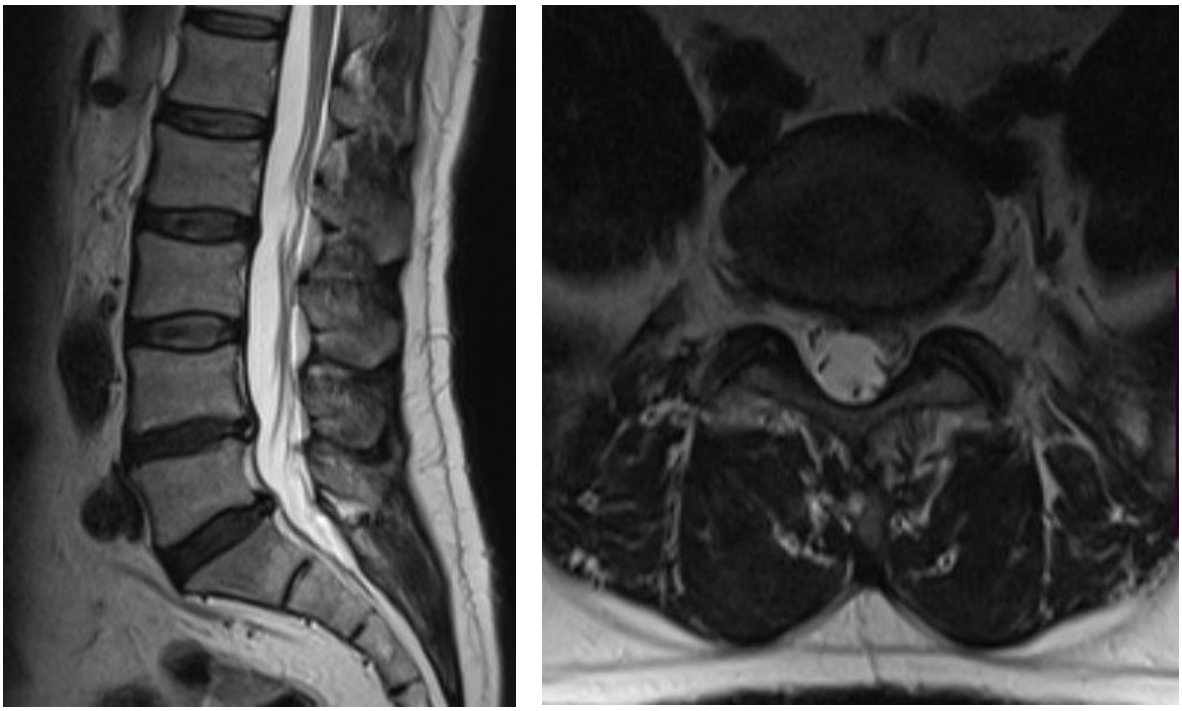

Figure 2. A) In the T2 weighted control MRI inspection, in sagittal section, L4-L5 level sequestrum disc fragment spontaneously regressed. B) In the T2 weighted control MRI inspection in axial section, L4-L5 level sequestrum disc fragment spontaneously regressed

Discussion

Many essays were published about the spontaneous regression of lumber disc hernia (5).

In the prospective MRI analysis they carried on, Bozzao et.al. showed that in %o63 of the cases, the disc protrusion regressed more than %70 (6).

In their prospective studies carried on 21 cases, Ocak et.al., stated that after 1.5 months, a regression was seen in 4 cases (%16) but this was not statically meaningful (7). Takada et.al. reported that in their prospective studies carried on over 42 cases, there was regression in 8 cases after 3 months (8). Matsubara et. al. reported that the hernia size shrinked over %20 (9).

The mechanisms that affect the disc regression are not surely known. Three possible mechanisms are asserted (10). First one is the dehydration theory. It is the regression of disc hernia due to gradual dehydration and shrinking (11). The second is inflammatory reaction and neovacularization. The disc hernia is conceived as a foreign body in spinal epidural area and inflammatory reaction activates by the autoimmune system (12,13,14). The third one is retraction theory, it is the re retraction of the disc hernia to a distance of intervertebral (3). Henmi and et.al. have shown that in disc hernias, the ones with bigger sizes shrink more than the ones with smaller sizes. As the reason for this, they reported that especially in cases younger than 40 years old, the big disc hernias contain more water (14).

The patient presented in this case is an example for the total resolution of the sequestrum disc hernia by medical treatment without surgical operation. In this case, the disc regression may have resorption due to inflammatory or dehydration. The initial treatment of lumbar disc hernias is the conservative treatment. It includes exercise, analgesic use and psychotherapy (15). The lumbar disc hernias are treated conservatively apart from the cases where there is cauda equine syndrome or progressive motor loss. The surgical treatment, on the other hand, should be considered in the cases if the patient does not response to conservative treatment and/or there is persistent waist and leg pain, or in the case of a cauda equine syndrome development, or starting of neurological deficits (16).

Conclusion

The spontaneous resolution of disc hernias should be considered and patients who would be taken to surgery should be selected properly. Especially in younger patients, apart from the situations that require urgent surgery, in the beginning treatment of lumbar disc hernia, conservative methods should be applied for 6 weeks. Except indications of urgent surgery, there is no need to rush for surgical treatment.

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Acute myeloid leukemia under lenalidomide therapy in a patient with multiple myeloma

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Abstract

A 53-year-old patient who had a 7 year history of multiple myeloma was diagnosed with high risk myelodysplastic syndrome while on lenalidomide treatment. Progression to acute myeloid leukemia has occurred during the following 4 months. Like our case, secondary primary malignancies (SPMs) can rarely complicate treatment of multiple myeloma. Although possible association between SPMs in patients receiving lenalidomide can be attributed to previous melphalan use, potential SPM risk with lenalidomide cannot still be ruled out safely

Key words: Multiple myeloma; Lenalidomide; Acute myeloid leukemia

Introduction

A 53-year-old woman was diagnosed with multiple myeloma (MM) in 2007. Autologous stem cell transplantation (ASCT) was performed after achieving complete remission (CR) with 4 cycles of vincristine-doxorubicin-dexamethasone (VAD) therapy. The patient was in CR after ASCT. The disease relapsed in 2012. Bortezomib and dexamethasone was initiated and partial remission was achieved after four cycles. Second ASCT was performed and the patient was followed up in CR for 2 years. Clinical relapse was observed within two years after the ASCT, treatment with lenalidomide and dexamethasone was initiated. During the fourth cycle, grade IV neutropenia, anemia, and thrombocytopenia was observed. The treatment was discontinued due to severe pancytopenia requiring routine transfusions. A bone marrow aspiration and biopsy was performed. Significant dysmorphic alterations in megakaryocytes, myeloid and erythroid cell lines were evident. Eight percent of all bone marrow cells were myeloblasts.

Clonal plasma cells were not observed. She was diagnosed with myelodysplastic syndrome, refractory anemia with excess blasts type I (MDS-RAEB1) and azacytidine treatment was initiated.

During the second cycle of azacytidine, patient was hospitalized for intravenous antibiotic treatment due to bacterial pneumonia. Azacytidine was interrupted for approximately two months. A repeat biopsy was performed, which revealed 53% myeloblasts consistent with a diagnosis of acute myeloid leukemia (AML).

Induction chemotherapy with idarubicin for three days and cytarabine for seven days were commenced. Bone marrow biopsy on the 28th day showed 13% myeloblasts. Patient died before salvage chemotherapy due to septicemia.

Discussion

In multiple myeloma, SPM incidence is about 6.1% per year in twenty years being comparable to expected incidence in general population. There is a correlation between long-term melphalan use and AML/MDS development (1).

According to the lenalidomide maintenance trial reported by Attal et al, SPM incidence in lenalidomide arm was 3.1 and 1.2 in placebo arm for every 100 patient years (p=0.002). Thirteen hematological malignancies in lenalidomide arm and 5 in placebo arm were reported. However number of AML and MDS cases was similar (2).

Similiarly, cumulative SPM incidence in the study reported by Mccarthy et al was 8% in lenalidomide arm and 3% in placebo arm. Eight cases of hematological malignancies were detected in lenalidomide arm and six of these eight cases were MDS or AML.

Only one hematological malignancy was detected in placebo arm (3). In another literature by Palumbo et al. 10 cases of MDS or AML were reported in lenalidomide arm corresponding to an incidence of 2.6%. (4).

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Table: Incidence of SPMs with lenalidomide according to the reported literature

Reference	Total number of patients	Randomised arms	Number of invasive SPMs	Number of hematologic malignancies	Number of MDS or AML
Attal et al. (2)	614	Lenalidomide	23	13	5
		Placebo	9	5	4
McCarthy et al. (3)	460	Lenalidomide	18	8	6
		Placebo	6	1	0
Palumbo et al. (4)	459	MPR-R*	12	7	5
		MPR	9	5	5
		MP	4	1	1

However, in all of these above mentioned literature which were also presented in the table, lenalidomide was incorporated into the induction with a melphalan-based chemotherapy, either used before ASCT, or given as maintenance therapy after ASCT or melphalan-based chemotherapy. Various studies reported safety data for lenalidomide regarding SPM incidence (5,6). The incidence of SPM is about 1.5-7.4%, which is comparable to SPM incidence in healthy population.

Conclusion

Although possible association between SPMs in patients receiving lenalidomide can be attributed to previous melphalan use, potential SPM risk with lenalidomide cannot still be ruled out safely.

Conflict of Interest: The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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