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When a drug, product, hardware, or software program is mentioned within the main text, product information, including the name of the product, the producer of the product, and city and the country of the company (including the state if in USA), should be provided in parentheses in the following format: "Discovery St PET/CT scanner (General Electric, Milwaukee, WI, USA)"

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Book section: Suh KN, Keystone JS. Malaria and babesiosis. Gorbach SL, Barlett JG, Blacklow NR,

editors. Infectious Diseases. Philadelphia: Lippincott Williams; 2004.p.2290-308.

Books with a single author: Sweetman SC. Martindale the Complete Drug Reference. 34th ed. London: Pharmaceutical Press; 2005.

Editor(s) as author: Huizing EH, de Groot JAM, editors. Functional reconstructive nasal surgery. Stuttgart-New York: Thieme; 2003.

Conference proceedings: Bengisson S. Sothemin BG. Enforcement of data protection, privacy and security in medical informatics. In: Lun KC, Degoulet P, Piemme TE, Rienhoff O, editors. MEDINFO 92. Proceedings of the 7th World Congress on Medical Informatics; 1992 Sept 6-10; Geneva, Switzerland. Amsterdam: North-Holland; 1992. pp.1561-5.

Scientific or technical report: Cusick M, Chew EY, Hoogwerf B, Agrón E, Wu L, Lindley A, et al. Early Treatment Diabetic Retinopathy Study Research Group. Risk factors for renal replacement therapy in the Early Treatment Diabetic Retinopathy Study (ETDRS), Early Treatment Diabetic Retinopathy Study KidneyInt: 2004. Report No: 26.

Thesis: Yılmaz B. Ankara Üniversitesindeki Öğrencilerin Beslenme Durumları, Fiziksel Aktivitelerive Beden Kitle İndeksleri Kan Lipidleri Arasındaki Ilişkiler. H.Ü. SağlıkBilimleriEnstitüsü, DoktoraTezi. 2007.

Manuscripts accepted for publication, not published yet: Slots J. The microflora of black stain on human primary teeth. Scand J Dent Res. 1974.

Epub ahead of print articles: Cai L, Yeh BM, Westphalen AC, Roberts JP, Wang ZJ. Adult living donor liver imaging. DiagnIntervRadiol. 2016 Feb 24. doi: 10.5152/dir.2016.15323. [Epub ahead of print].

Manuscripts published in electronic format: Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis (serial online) 1995 Jan-Mar (cited 1996 June 5): 1(1): (24 screens). Available from: URL: http:/ www.cdc.gov/ncidodlElD/cid.htm.

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RESEARCH / ARAŞTIRMA
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COMPARISON OF POSTOPERATIVE AND ONCOLOGICAL OUTCOMES IN ROBOTIC AND OPEN RIGHT COLECTOMY FOR COLON CANCER

KOLON KANSERİNDE ROBOTİK VE AÇIK SAĞ KOLEKTOMİNİN POSTOPERATİF VE ONKOLOJİK SONUÇLARININ KARŞILAŞTIRILMASI

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ABSTRACT

Objective: This study aims to compare the short-term outcomes of robotic right hemicolectomy for right-sided colon cancer to those of conventional open right hemicolectomy.

Material and Method: Patients who underwent surgical treatment for right-sided colorectal cancer between 2020 and 2022 were included in the study. Patients had been divided into two groups: Group 1, who underwent conventional surgery, and Group 2, who underwent robotic surgery. Clinical data and preoperative findings of patients were compared between the groups.

Result: A total of 51 patients participated in our study. Group 1 consisted of 39 patients and Group 2 consisted of 12 patients. The mean age was 60.7 vs. 62.3 (p=0.773). No conversions or intraoperative complications occurred. Extended right hemicolectomy was performed in 23.1% vs. 8.36% (p=0.083). The operation time was longer in Group 2 (2.84 vs. 3.04, p=0.023). One patient in Group 1 underwent reoperation for ileus during the postoperative period. T3-stage tumors (48.7% vs. 50%, p=0.794) and N0 lymph node metastasis (38.5% vs. 41.7%, p=0.827) were detected most frequently. The total number of lymph nodes dissected was 37.2 vs. 41.9 (p=0.179). The number of malignant lymph nodes was 2.54 vs. 6.42 (p=0.881). The most common Clavien-Dindo score was 1 in both groups (79.5% vs. 83.3%, p=0.339). The length of stay was similar between the groups (6.38 vs. 5.92, p=0.156). Readmission occurred in 6 patients in Group 1, with reasons being anastomotic leakage, ileus, and general condition disorder.

ÖZET

Amaç: Bu çalışma, sağ kolon kanseri için robotik sağ hemikolektominin kısa vadeli sonuçlarını konvansiyonel sağ hemikolektomiyle karşılaştırmayı amaçlamaktadır.

Gereç ve Yöntem: 2020-2022 yılları arasında sağ taraf yerleşimli kolorektal kanser nedeniyle cerrahi tedavi uygulanan hastalar çalışmaya dahil edildi. Hastalar konvansiyonel cerrahi geçirenler Grup 1, robotik cerrahi uygulananlar Grup 2 olmak üzere 2 gruba ayrıldı. Bu gruplarda hastalara ait klinik veriler ve peroperatif sonuçlar karşılaştırıldı.

Bulgular: Çalışmamıza 51 hasta katıldı. Grup 1 39 hastadan, Grup 2 12 hastadan oluşuyordu. Yaş ortalaması (60,7 ve 62,3 p=0,773) idi. Hiçbir dönüşüm veya intraoperatif komplikasyon oluşmadı. Genişletilmiş sağ hemikolektomi (%23,1 ve %8,36 p=0,083) oranında uygulandı. Operasyon süresi Grup 2'de uzundu (2,84 ve 3,04 p=0,023). Grup 1'de bir hasta postoperatif dönemde ileus nedeniyle tekrar ameliyat edildi. En sık T3 evre tümörler (%48,7 ve %50, p=0,794) ve N0 (%38,5 ve %41,7, p=0,827) saptanmıştı. Lenf nodu diseksiyonu sayıları total lenf nodları 37,2 ve 41,9 (p=0,179) ve malign nodlar 2,54 ve 6,42 (p=0,881) idi. En sık görülen Clavien-Dindo skoru her iki grupta da 1 idi (%79,5 ve %83,3, p=0,339). Yatış süresi gruplarda benzerdi (6,38 ve 5,92, p=0,156). Grup 1'de 6 hastada hastaneye tekrar başvuru görüldü. Başvuru sebepleri anastomoz kaçağı, ileus ve genel durum bozukluğu idi.

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Conclusion: Our experience shows the feasibility and safety of robotic surgery for the treatment of right-sided colon cancer. This method has provided satisfactory short-term outcomes.

Keywords: Colorectal cancer, robotic surgery, right colectomy, postoperative complications, oncologic outcomes

Sonuç: Deneyimlerimiz sağ kolon kanserinin tedavisi için robotik cerrahinin fizibilitesini ve güvenliğini doğrulamaktadır. Bu yöntem tatmin edici kısa vadeli sonuçlar sağlamıştır.

Anahtar Kelimeler: Kolorektal kanser, robotik cerrahi, sağ kolektomi, postoperatif komplikasyon, onkolojik sonuçlar

INTRODUCTION

Over the past few decades, medicine and surgery have made unprecedented strides in technology. Historically, these advances were driven purely by science; however, today, industry interests have become powerful drivers of development. Rapid advancements in minimally invasive surgical technology are both challenging and fascinating, making it difficult to distinguish between passing trends and scientific evidence (1).

Colorectal cancer is the third most common malignancy and the second leading cause of cancer deaths worldwide. In 2020, there were 1.9 million cases, with an estimated 0.9 million deaths globally (2). Surgery remains the cornerstone of treatment. Right colectomy is a procedure frequently performed by general and colorectal surgeons to treat malignancies of the cecum, right colon, and hepatic flexure. In contemporary times, the most appropriate surgical approach for these resections is often debated (3).

Minimal invasive (MI) surgery is gaining acceptance as the treatment choice of colorectal cancer worldwide. Numerous non-oncological quality-of-life advantages have been reported over the conventional open approach, with less postoperative pain, shorter inpatient duration, faster return to daily activities, and better cosmetic outcomes. Long-term oncological outcomes have been found to be at least equivalent to the traditional surgical approach (4-6).

Robotic surgical platforms, such as the da Vinci surgical system, have been designed to address many of the limitations of laparoscopic surgery. Some of the advantages provided include a stable three-dimensional view directly controlled by the operating surgeon, elimination of tremors, improved ergonomics, and 180° articulation with a 540° rotation for a wider range of motion. However, there has been widespread criticism of robotic right hemicolectomy (RRH), including increased cost and longer operation time, as well as the inartificial advantages of robotic platforms being less remarkable in the larger intra-abdominal cavity compared to the pelvis, and impaired ergonomics and range of motion due to instrument collision (7,8).

A review of the literature reveals that robotic surgery is more frequently applied in rectal cancer due to these reasons, and comparative studies on the use of robots in colorectal cancer often involve rectal cancer cases. There are limited trials in the literature on the occupation of robots in right colon cancer (3-6).

In our study, we aimed to present the experience of a newly established robotic surgery center in a tertiary hospital by comparing right hemicolectomy experiences with the conventional method, considering the existing literature.

MATERIAL and METHODS

After obtaining approval from Basaksehir Cam and Sakura City Hospital Local Ethics Committee (Date: 26.01.2022, No: 30), patients who underwent surgical resection for colorectal cancer between 2020 and 2022 were included in our study. Patients under 18 years of age, those who underwent laparoscopic surgery, those with benign pathology results, and those with non-adenocarcinoma malignancies were excluded from the study. A retrospective analysis was conducted using a prospective database created from nurse observation forms, anesthesia records, and pathology reports in the Electronic Health Record system.

Patients were separated into two groups based on the surgical technique used: Group 1 underwent conventional surgery, and g+roup 2 underwent robotic surgery. We compared demographic data, American Society of Anesthesiologists (ASA) scores, preoperative tumor marker levels, hemoglobin and albumin levels, neoadjuvant treatment status, and tumor location for these groups. Additionally, intraoperative complications, conversion, operation time, and histopathological parameters such as tumor diameter, total number of dissected and metastatic lymph nodes, distance to the surgical margin, and TNM stage were assessed. Postoperative quality indicators, including hospital stay duration, 90-day reoperation, 90-day readmission, 30-day postoperative mortality, Clavien-Dindo complication severity, and adjuvant treatment status, were also recorded.

Surgical indications were determined for all patients at the institutional multidisciplinary meeting discussion.

Preoperative colonoscopy image evaluation and thorax-abdominal-pelvic computed tomography (CT) scans were routinely performed for all patients, with Positron Emission Tomography and CT (PET-CT) scans performed when deemed necessary. Fast-track protocols were attempted for each patient. The pathological stage of the disease was determined according to the TNM Classification (8,9). Unplanned reoperations were considered as surgical procedures under general, spinal, or epidural anesthesia within 90 days of the index operative procedure for any reason, excluding follow-up procedures based on pathology results, in accordance with the The American College of Surgeons (ACS) National Surgical Quality Improvement Program (NSQIP) definition (10). Conversion to open surgery was defined as completing any part of the procedure with the open technique, except for the removal of the surgical specimen. The operative time was defined as the duration from the first skin incision to the final closure of the abdominal wall. The Clavien-Dindo classification was used to define and grade postoperative complications (11).

Surgical procedures

The preference for the robotic technique was based merely on the availability of the robotic system and the surgeon's preference. All robotic operations were performed by a single surgeon. On the day before the operation, all patients underwent mechanical bowel preparation and received antibiotic prophylaxis with ceftriaxone (2 g IV) and metronidazole (500 mg IV) just prior to the surgery. In both groups, a Foley catheter and a nasogastric tube were routinely placed in the operating room following the induction of general anesthesia.

The same surgeon performed all robotic operations using the Da Vinci Xi Surgical System (Intuitive Surgical Inc., Sunnyvale, CA, USA).

Pneumoperitoneum was created by puncturing the patients' umbilicus with a Veress needle, achieving an intra-abdominal pressure of 10 mmHg. An 8 mm robotic port was placed in the midline suprapubic area, and all intra-abdominal quadrants were examined with a 30-degree optic to exclude peritoneal metastases. The other three robotic ports were placed under direct vision, aligned to form a straight line between the suprapubic robotic port and the left arcus costa, and spaced 6-10 cm apart. A 10 mm laparoscopic port, to be used by the assistant surgeon for clipping, linear endostapler, aspiration, gauze, and suture insertions and removals, was placed in the left lower quadrant, forming a triangle with the two robotic ports on the left side of the abdominal wall. After placing the ports, patients were positioned in a 15-degree reverse Trendelenburg position. The Da Vinci Surgical System was brought to the operating table from the patients' right side.

Robotic colon resections were performed in defined standard steps. Right hemicolectomy or extended right hemicolectomy was chosen based on tumor location. All patients underwent complete mesocolic excision (CME). During the medial dissection step of the ascending colon, the ileocolic artery and vein, superior mesenteric vein (SMV), and superior mesenteric artery (SMA) were dissected with Monopolar Curved Scissors (Intuitive da Vinci Robotic Surgical Systems) and clipped with Hem-o-lok. The dissection of the mesocolon continued in a caudo-cranial direction, and the right colic artery and vein were clipped with Hem-o-lok and cut. Right branches of the middle colic artery and vein in patients with ascending colon tumors were clipped with Hem-o-lok during the cranio-caudal mesocolic dissection, and right branches of the middle colic artery and vein in patients with hepatic flexure or transverse colon tumors were clipped with Hem-o-lok, freeing the colonic mesentery. The posterior mesocolon was dissected from medial to lateral, preserving the perirenal fascia. During lateral dissection of the ascending colon, Toldt's fascia was incised from the hepatic peritoneal attachment to the pelvic peritoneal space. The gastrocolic ligament was cut from the right half of the transverse colon for hepatic flexure mobilization. The mesocolon was dissected over the pancreas and duodenum, and encountered branches of the Henle trunk were clipped and cut. In hepatic flexure and transverse colon tumors, the greater omentum was removed along with the colon segment to be respected.

The proximal resection margin for all patients was set as the terminal ileum, 5-10 cm proximal to the ileocecal valve. In patients with colon tumors, the transverse colon's proximal blood supply was deemed adequate for the distal resection margin. For patients with hepatic flexure tumors and transverse colon tumors, the distal region of the transverse colon was chosen as the site with sufficient blood supply. The distal and proximal borders of the mesocolon were cut using Monopolar Curved Scissors and Maryland Bipolar Forceps (Intuitive da Vinci Robotic Surgical Systems). Colon and ileum resections were performed with an Endo stapler using a 10 mm assistant port. The specimen was removed through a mini-incision made in the median supra-umbilical region using an Alexis Wound Protector-Retractor (Applied Medical).

During the anastomosis stage, an anvil was inserted into the anti-mesenteric wall of the distal ileum. The ileocolic anastomosis was performed extracorporeally by placing the circular stapler in the transverse colon.

For patients who underwent conventional surgery, all steps were performed openly with a median incision above and below the umbilicus.

Statistical analysis

The SPSS SPSS ver. 23.0 (IBM Corp., Armonk, NY) software was used for the statistical analysis of the data. Cat-

egorical measurements were summarized as numbers and percentages, while continuous measurements were presented as mean and standard deviation (median and minimum-maximum where appropriate). The chi-square test was employed for the analysis of categorical variables. The Shapiro-Wilk test was utilized to determine whether the parameters in the study exhibited a normal distribution. For parameters that did not demonstrate a normal distribution, the Mann-Whitney U test was used in paired group analysis. The statistical significance level for all tests was set at 0.05.

RESULTS

A total of 51 patients participated in our study, with Group 1 consisting of 39 patients and Group 2 comprising 12 patients. The male gender was predominant in both groups (74.4% vs. 58.3%, p=0.287). The mean ages were 60.7 and 62.3 (p=0.773). The most common ASA score was 2 in both groups (22% vs. 10%, p=0.317). Tumor localization in the ascending colon was more frequent in both groups (46.2% vs. 58.3%, p=0.726). Demographic and clinical data can be found in Table 1.

In Group 1, four patients had mucinous adenocarcinoma. The most common tumor grade was G2 in both groups (82.1% vs. 66.7%, p=0.553). Macroscopic tumor perforation (p=0.942), presence of lymphovascular invasion (p=0.202), presence of perineural invasion (p=0.696), and tumor budding presence (p=0.338) were similar between the groups. T3 stage tumors (48.7% vs. 50%, p=0.794) and N0 lymph node metastases (38.5% vs. 41.7%, p=0.827) were the most frequently detected pathological features. The largest mean tumor diameters were 52.5 mm and 68.7 mm (p=0.135). The total number of lymph nodes dissected was 37.2 and 41.9 (p=0.179). The number of malignant lymph nodes was 2.54 and 6.42 (p=0.881). Pathological features are displayed in Table 2.

Extended right hemicolectomy was performed in 23.1% and 8.36% of patients (p=0.083). The operation time was longer in Group 2 (2.84 vs. 3.04, p=0.023). No intraoperative complications or conversions to open surgery occurred in any patients. One patient in Group 1 underwent reoperation for ileus in the postoperative period. In both study groups, the most frequently observed Clavien-Dindo classification was grade 1 (79.5% vs. 83.3%, p=0.339). The length of hospital stay was similar between the groups (6.38 vs. 5.92, p=0.156). Readmission occurred in 6 patients from Group 1, with causes including anastomotic leakage, ileus, and general condition disorder. The

Table 1: Demographic characteristics and preoperative findings of the patients

	Open (n=39)	Robotic (n=12)	Total (n=51)	p
	n (%)	n (%)	n (%)	
Gender				
Male	29 (74.4)	7 (58.3)	36 (70.6)	0.287[a]
Female	10 (25.6)	5 (41.7)	15 (29.4)	
Age mean±SD	60.7±14.3	62.3±14.1	61.1±14.1	0.773[b]
ASA score				
1	5 (12.8)	-	5 (9.8)	0.317[a]
2	22 (56.4)	10 (83.3)	32 (62.7)	
3	10 (25.6)	2 (16.7)	12 (23.5)	
4	2 (5.1)	-	2 (3.9)	
CEA (µg/L) (mean±SD)	25.3±104.8	9.12±10.7	23.1±97.2	0.766[b]
CA 19.9 (U/ml) (mean±SD)	154.4±756.7	17.6±11.7	135.9±703.8	0.982[b]
Hemoglobin (g/dl) (mean±SD)	10.9±1.8	10.6±1.6	10.9±1.7	0.526[b]
Albumin (g/dl) (mean±SD)	39.2±5.5	40.0±3.9	39.4±5.1	0.760[b]
Tumor localization				
Caecum	12 (30.8)	3 (25)	15 (29.4)	0.726[a]
Ascending colon	18 (46.2)	7 (58.3)	25 (49)	
Hepatic flexura	6 (15.4)	2 (16.7)	8 (15.7)	
Transverse colon	3 (7.7)	-	3 (5.9)	

* p<0.05, [a]: Chi-square, [b]: Mann Whitney U, ASA: American Society of Anesthesiology, CEA: Carcinoembryonic antigen, CA: Cancer antigen

Table 2: Pathological findings of study groups

	Open (n=39)	Robotic (n=12)	Total (n=51)	p
	n (%)	n (%)	n (%)	
Type of tumor				
Adenocarcinoma	34 (87.1)	12 (100)	46 (90.2)	0.426[a]
Mix adenocarcinoma	1 (2.6)	-	1 (2)	
Mucinous adenocarcinoma	4 (10.3)	-	4 (7.8)	
Tumor grade (Differentiation)				
G1	3 (7.7)	2 (16.7)	5 (9.8)	0.553[a]
G2	32 (82.1)	8 (66.7)	40 (78.4)	
G3	3 (7.7)	2 (16.7)	5 (9.8)	
G4	1 (2.6)	-	1 (2)	
Presence of macroscopic tumor perforation	3 (7.7)	1 (8.3)	4 (7.8)	0.942[a]
Presence of lymphovascular invasion	29 (74.4)	11 (91.7)	40 (78.4)	0.202[a]
Presence of perineural invasion	17 (43.6)	6 (50)	23 (45.1)	0.696[a]
Presence of tumor budding	27 (69.2)	10 (83.3)	37 (72.5)	0.338[a]
T stage				
T2	4 (10.3)	2 (16.7)	6 (11.8)	0.794[a]
T3	19 (48.7)	6 (50)	25 (49)	
T4	16 (41)	4 (33.3)	20 (39.2)	
N stage				
N0	15 (38.5)	5 (41.7)	20 (39.2)	0.827[a]
N1a	3 (7.7)	-	3 (5.9)	
N1b	11 (28.2)	3 (25)	14 (27.5)	
N2a	6 (15.4)	3 (25)	9 (17.6)	
N2b	4 (10.3)	1 (8.3)	5 (9.8)	
Closest tumor margin (proximal or distal) mm (mean±SD)	102.4±43.7	78.8±22.9	96.8±40.9	0.074[b]
Widest tumor diameter mm (mean±SD)	52.4±25.6	68.7±32.6	56.2±27.9	0.135[b]
No. of total lymph nodes (mean±SD)	37.2±19.6	41.9±9.9	38.3±17.8	0.179[b]
No. of malign lymph nodes (mean±SD)	2.54±3	6.42±15.2	3.45±7.8	0.881[b]

* $p<0.05$, [a]: Chi-square, [b]: Mann Whitney U

rates of receiving adjuvant treatment were similar in the groups (82.1% vs. 75%, p=0.591). The perioperative and postoperative periods are presented in Table 3.

DISCUSSION

In our study comparing robotic right hemicolectomy (RRC) with conventional right hemicolectomy (CRC), we found that robotic colorectal resections using a robotic platform are as safe as performing a conventional RRC when appropriate training and experience are available. Our findings showed comparable morbidity rates to those observed with CRC, adequate lymph node dissection, and despite the longer operation time, no increased morbidity was detected.

A 2016 study from Denmark reported a conversion rate of around 20% in patients undergoing minimally invasive CME, with a 9.1% intraoperative organ injury and a 6.2% mortality rate observed in the entire series (12). Although the results of this study may cause surgeons to approach with caution, centers around the world have shown lower levels of morbidity in their studies than initially reported (13,14). In their study comparing robotic and convention-

Table 3: Perioperative and postoperative clinical outcomes

	Open (n=39)	Robot (n=12)	Total (n=51)	p
	n (%)	n (%)	n (%)	
Type of surgery				
Extended right hemicolectomy	9 (23.1)	1 (8.36)	10 (19.6)	0.083[a]
Right hemicolectomy	29 (74.4)	11 (91.7)	40 (78.4)	
Right hemicolectomy + liver metastasectomy	1 (2.6)	-	1 (2.0)	
Operation time (hours) (mean±SD)	2.84±2.9	3.04±0.9	2.89±2.6	**0.023*[,b]**
Reoperation	1 (2.6)	-	1 (2.0)	0.575[a]
Clavien Dindo Score				
1	31 (79.5)	10 (83.3)	41 (80.4)	0.339[a]
2	4 (10.3)	1 (8.3)	5 (9.8)	
3a	2 (5.1)	-	2 (3.9)	
3b	-	1 (8.3)	1 (2.0)	
5	2 (5.1)	-	2 (3.9)	
Length of stay (days) (mean±SD)	6.38±3.0	5.92±2.5	6.27±2.9	0.156[b]
Readmission 90 days	6 (15.4)	-	6 (11.6)	0.148[a]
30-days mortality	2 (5.1)	-	2 (3.9)	0.424[a]
Adjuvant treatment	32 (82.1)	9 (75.0)	41 (80.4)	0.591[a]

* p<0.05, [a]: Chi-square, [b]: Mann Whitney U

al methods for right colon cancer, Larach et al. did not report any conversions and found a similar overall complication rate in the postoperative period, indicating that this allowed for enhanced postoperative recovery (15). Hirschburger et al.'s study showed that the robotic approach was superior to conventional methods in terms of postoperative complication rates, particularly wound infections, and shorter hospital stays (16). In our series, no conversions were reported, and although the operation time was longer in the robot group, it did not affect the postoperative period. We did not identify a specific complication or reason for re-admission due to robot use.

Regarding cancer management, oncological standards defined mainly by open surgical techniques should be taken into account. In terms of the intestinal, mesorectal, and mesocolic envelopes, the resected specimen should be left intact. The resection margins should be appropriate and preferably exceed negative margins. Ideally, the margins should be greater than 5 cm. The technique should also allow for adequate lymph node uptake for staging and therapeutic purposes, with more than 12 lymph nodes for every anatomical segment (17,18). The current literature suggests that there is a higher lymph node harvesting efficiency in minimally invasive robotic surgery for CME performed in RRC cases, but there is insufficient evidence on this topic (16,19). There are also studies reporting a lower number of lymph nodes in robotic surgery despite having an adequate number (15). In our series, the number of lymph nodes harvested and the distances to the surgical margin were sufficient in both groups, which we attributed to the experience of the robotic surgery team in laparoscopy.

Financial constraints in modern medicine require considering the implementation and maintenance costs of new technology alongside patient outcomes. Cost analyses in studies are challenging due to numerous factors affecting the cost both directly and indirectly. Another study examining the largest hospital-based comparative databases in the United States, with 17,265 laparoscopic and 744 robotic procedures, found that robotic surgery was associated with a $5,272 higher total hospitalization cost and $4,432 direct cost compared to laparoscopic surgery (20). Consequently, it is justifiable to assume that robotic surgery may not be a cost-effective option under prevailing circumstances.

Several studies in the literature have reported long-term oncological outcomes of robotic right hemicolectomy in different patient populations. Spinoglio et al. reported disease-specific survival rates of 94.5%, disease-free survival rates of 91.4%, and overall survival rates of 90.3% in their series of 100 patients undergoing CME with robotic right hemicolectomy, during a median follow-up period of 48.5 months

(range, 24-114 months) (6). In the pilot studies of Huscher et al., which included 123 patients undergoing robotic right hemicolectomy, the median follow-up period was 39 months (IQR, 25-55), with a median overall survival of 69 months (95% CI, 57-80) and a mean disease-free survival of 67 months (95% CI, 65-68) (21). However, the literature currently lacks sufficient evidence to support the claim that robotic surgery provides a survival advantage for right colon cancer. In our series, we were unable to present long-term oncological outcomes due to insufficient patient follow-up periods.

The major limitation of this study was the limited quantity of patients and its retrospective nature. Additionally, as our center is newly established, we could not present long-term oncological results and cost analyses.

CONCLUSION

In our study, we compared robotic surgery and conventional surgery with similar dissection widths and comparable morbidity profiles. To confirm these results and obtain long-term oncological outcomes, prospective multicenter studies are necessary.

Ethics Committee Approval: This study was approved by Basaksehir Cam and Sakura City Hospital Local Ethics Committee (Date: 26.01.2022, No: 30)

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PANCREATITIS IN GALLSTONE PATIENTS: IS THERE ANY LINK BETWEEN DIET AND DISEASE?

SAFRA TAŞI HASTALARINDA PANKREATİT: DİYET İLE HASTALIK ARASINDA BİR BAĞLANTI VAR MI?

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ABSTRACT

Objective: Acute pancreatitis is most often caused by gallstones. There is no clear relationship between diet and gallstone pancreatitis. The purpose of this research was to examine dietary differences in pancreatitis patients with gallstones.

Material and Method: Patients with acute biliary pancreatitis and patients with gallstones without pancreatitis were included in this prospective case-control study. Groups were set to be similar in case numbers, age, gender, and gallbladder stone size. A three-day food consumption questionnaire and a food consumption frequency questionnaire were applied to all volunteers. The BeBis 8 Full version program was used to evaluate body mass index, alcohol and cigarette consumption status, daily physical activity status, eating frequency, and food consumption status.

Result: A total of 120 patients, including 60 patients who developed pancreatitis due to gallstones, and 60 patients who only had gallstones were included in the study. Among the demographic data, monthly income was statistically higher in pancreatitis. In addition, it was found that the daily milk-yoghurt, red meat, chicken, salami-sausage, egg, rice-pasta, protein, fat, and cholesterol intakes of patients with pancreatitis were significantly higher. In the multivariate logistic regression analysis, it was determined that the increase in daily milk-yoghurt, egg, rice-pasta and protein intake were independent risk factors.

Conclusion: Reducing the consumption of red meat, eggs, fat, cholesterol, milk-yoghurt, rice and pasta, salami and sausage in people with gallstones may reduce the incidence of acute pancreatitis in these individuals.

Keywords: Gallstone, pancreatitis, diet, red meat, egg

ÖZET

Amaç: Akut pankreatiti genellikle safra taşlarından kaynaklanır. Diyet ile safra taşı pankreatit arasında net bir ilişki bulunmamaktadır. Bu araştırmanın amacı, safra taşı olan pankreatit hastalarında beslenme farklılıklarını incelemektir.

Gereç ve Yöntem: Bu prospektif vaka-kontrol çalışmasına akut biliyer pankreatiti olan hastalar ve pankreatit gelişmemiş safra taşı olan hastalar dahil edilmiştir. Gruplar, vaka sayıları, yaş, cinsiyet ve safra kesesi taşı büyüklüğü açısından benzer olarak belirlendi. Tüm gönüllülere üç günlük besin tüketim formu ve besin tüketim sıklığı formu uygulandı. Vücut kütle indeksi, alkol ve sigara tüketimi durumu, günlük fiziksel aktivite durumu, yeme sıklığı ve besin tüketim durumunu değerlendirmek için BeBis 8 Full versiyon programı kullanıldı.

Bulgular: Çalışmaya, safra taşları nedeniyle pankreatit gelişen 60 hasta ve pankreatit gelişmemiş safra taşı olan 60 hasta olmak üzere toplam 120 hasta dahil edildi. Demografik veriler arasında aylık gelir pankreatit gelişenlerde istatistiksel olarak daha yüksek bulundu. Ayrıca, pankreatitli hastaların günlük süt-yoğurt, kırmızı et, tavuk, salam-sosis, yumurta, pirinç-makarna, protein, yağ, kolesterol alımlarının anlamlı olarak daha yüksek olduğu tespit edildi. Çok değişkenli lojistik regresyon analizinde, günlük süt-yoğurt, yumurta, pirinç-makarna ve protein alımındaki artışın bağımsız risk faktörleri olduğu belirlendi.

Sonuç: Safra taşı olan bireylerde kırmızı et, yumurta, yağ, kolesterol, süt-yoğurt, pirinç ve makarna, salam ve sosis tüketiminin azaltılması, akut pankreatit insidansını bu kişilerde azaltabilir.

Anahtar Kelimeler: Safra taşı, pankreatit, diyet, kırmızı et, yumurta

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INTRODUCTION

There is an annual incidence of 4.9-35 cases of acute pancreatitis (AP) in every 100,000 people and it increases with the rise of obesity and gallstones (1). Age-related incidence is most prevalent between 30-60, and gender-specific incidence does not differ. Acute pancreatitis is usually caused by gallstones, followed by alcohol and drug abuse and other factors (2).

There is some evidence that diet and obesity contribute to the development of gallstones, although the relationship between AP and diet is not fully understood. Patients with obesity have been reported to have a two-fold increased risk of developing gallstones than a body mass index (BMI) of 20-25 in people of normal weight (3). A number of studies have also demonstrated that gallstone is associated with the consumption of refined carbohydrates and triglycerides in the diet, as well as the reduction of dietary fibre (4).

In the literature, limited information is available about the relationship between diet and AP. Moreover, there is often a lack of clarity in the literature about whether patients with acute, chronic, or recurrent pancreatitis or whether pancreatitis develops due to gallbladder stones. As reported in Sarles' 1973 study, high fat and protein consumption as well as alcohol consumption increase the risk of pancreatitis, not being associated with the etiological cause (5). There have been few studies that examined whether the proteins, fats, and carbohydrates are associated with alcohol-related or gallstone-related AP, or whether mortality is related to AP (6-8).

In addition, coffee, consumption of small amounts of fruit, and increased consumption of freshwater fish and boiled rice are among the other etiological factors accused of diet in the development of AP (9-11). It has also been reported that extremely large meals after prolonged fasting (approximately 2000 kcal) and food allergies are risk factors for AP (12,13).

Although there are studies evaluating the relationship between diet and the development of non-biliary pancreatitis or the formation of gallstones AP the number of studies evaluating the role of diet in patients with gallstones pancreatitis in patients with gallstones is very limited. The aim of this study is to determine diet-related factors that may affect the development of ABP in patients with gallstones.

MATERIAL and METHODS

This case-control study was conducted prospectively between June 2021 and December 2021 following approval from the Local Human Ethics Committee (Date: 02.10.2020, No:2530). In addition to the patients hospitalized with the diagnosis of ABP in the general surgery unit, the patients who underwent cholecystectomy due to gallstones in the general surgery unit in the same period as the control group were included in the study. The study has been registered to ClinicalTrials.gov with the number NCT05142657. Informed consent was obtained from all volunteers.

The ABP group included people between 18 and 80 years old, with gallbladder stones and pancreatitis, while the exclusion criteria were cancer, pregnancy, chronic liver or kidney disease, mechanical icterus, and pancreatitis due to endoscopic retrograde cholangiopancreatography (ERCP). Inclusion criteria for the gallstone group were the same as the pancreatitis group except diagnosed with pancreatitis; exclusion criteria were having pancreatitis history and the other pancreatitis group exclusion criteria. Written consent forms were obtained from all of the volunteers. Patients were evaluated in order of hospitalization, and the study was stopped when there were 60 volunteers who met the inclusion-exclusion criteria in each group (Figure 1).

The ABP was diagnosed if the patient met two of the three criteria (sudden onset of pain in the upper abdomen, increasing pancreatic enzymes threefold or more than normal limits in the serum, detection of oedema and inflammation in the pancreas by imaging methods).

Three-day food consumption record and food consumption frequency form was applied to all volunteers. Additionally, the age, gender, BMI, alcohol consumption and smoking, daily physical activity, and eating frequency were noted. BeBis 8 computer program was used for the food consumption calculations and the data were compared between groups.

Statistical analysis was performed with SPSS 22.0 (IBM, Armonk, NY, USA) software. Descriptive statistics included the mean, standard deviation, and rate for numerical variables. Kolmogorov-Smirnov tests were

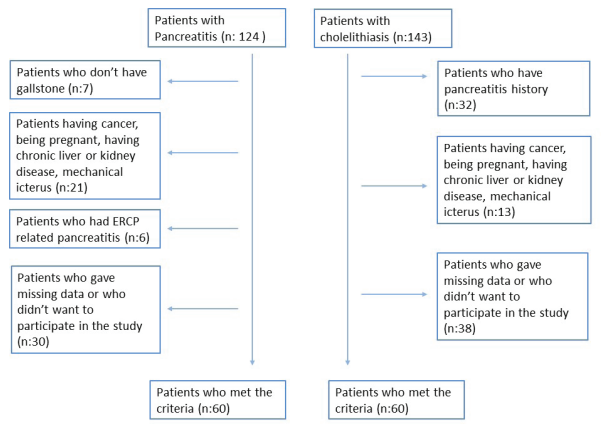

Figure 1: Flow diagram of gallstone cases with and without pancreatitis

used to confirm a normal distribution condition, normally distributed parameters were analysed with the Student T-test and non-normally distributed parameters were analysed with the Mann-Whitney U test. The Chi-Square test was used for categorical variables. Multivariate logistic regression tests were used for the evaluation of the level of impact. The statistical significance level was set at $p<0.05$.

RESULTS

A total of 120 volunteers were included in the study. There are two groups which have 60 patients who developed pancreatitis due to gallstones and 60 patients who only had gallstones and did not develop pancreatitis. The mean age of the volunteers was 53.33±14.90 years and the female/male ratio was 79/41.

When the demographic data, eating and exercise behaviours of the groups were evaluated, it was observed that the monthly income of the patients who had pancreatitis was higher than the patients who did not (p:0.000), and there was no significant difference in other parameters (Table 1).

When the dietary behaviours and food consumption of the participants in the study are evaluated, the intakes of daily milk-yoghurt, daily red meat, daily chicken, daily salami- sausage, daily egg, daily rice-pasta, daily protein, daily fat, daily cholesterol are significantly higher in patients with pancreatitis compared to those who do not. (p=0.006, p=0.019, p=0.000, p=0.043, p=0.000, p=0.000, p=0.000, p=0.029, p=0.015, respectively) (Table 2).

In multivariate logistic regression analyses for pancreatitis, it has been determined that the increase in daily

Table 1: The demographic data and the meal information of the patients according to groups

		Pancreatitis group (n=60)	Gallstone group (n=60)	p value
Gender (n-%)	Female	44 (73.3%)	35 (58.3%)	0.123
	Male	16 (26.7%)	25 (41.7%)	
Age (year±SD)		54.86±18.12	52.81±11.69	0.463
Gallstone size (mm) (median, min-max)		0.75 (0.2-2.4)	0.8 (0.2-2.9)	0.211
BMI (median, min-max)		27.90 (20.80-52.00)	27.69 (22.30-34.40)	0.342
Cigarette (n-%)	No	42 (70.0%)	31 (51.7%)	0.120
	Quit	9 (15.0%)	15 (25.0%)	
	Yes	9 (15.0%)	14(23.3%)	
Alcohol (n-%)	Yes	54 (90.0%)	55 (70.0%)	
	No	6 (10.0%)	5 (91.7%)	
Education level (n-%)	Non-literate	5 (8.3%)	1 (8.3%)	0.752
	Literate	6 (10.0%)	6 (10.0%)	
	Primary school	36 (60.0%)	33 (55.0%)	
	High school	9 (15.0%)	12 (20.0%)	
	University	4 (6.7%)	8 (13.3%)	
Monthly income ($) (n-%)	<150$	6 (10.0%)	30 (50.0%)	**0.000**
	150-300$	38 (63.3%)	20 (33.3%)	
	>300$	16 (26.7%)	19 (16.7%)	
Regular physical activity (at least 30 min/week) (n-%)	Yes	10 (16.7%)	11 (18.3%)	0.810
	No	50 (83.3%)	49 (81.7%)	
Regular breakfast (n-%)	Yes	58 (96.7%)	59 (3.3%)	0.559
	No	2 (98.3%)	1 (1.7%)	
Skipping mean meal in a day (n-%)	Yes	33 (55.0%)	25 (41.7%)	0.144
	No	27 (45.0%)	35 (58.3%)	

BMI: Body mass index, SD: Standard deviation

Table 2: Daily food habits according to pancreatitis existence

	Pancreatitis group (n=60)	Gallstone group (n=60)	p value
Daily milk-yoghurt (ml) (median, min-max)	151.00 (42.90-328.60)	128.55 (0.00-350.00)	**0.006**
Daily cheese (g) (median, min-max)	47.90 (0.00-114.30)	60.00 (5.00-114.30)	0.061
Daily red meat (g) (median, min-max)	21.40 (3.30-57.10)	14.00 (0.00-61.40)	**0.019**
Daily chicken (g) (median, min-max)	57.10 (0.00-128.60)	28.60 (0.00-64.30)	**0.000**
Daily fish (g) (median, min-max)	15.45 (0.00-271.40)	10.00 (0.00-71.40)	0.662
Daily salami-sausage (g) (median, min-max)	9.00 (0.00-85.70)	5.15 (0.00-41.60)	**0.043**
Daily giblets (Liver, kidney etc.) (g) (median, min-max)	0.00 (0.00-84.70)	0.00 (0.00-42.80)	0.850
Daily egg (g) (median, min-max)	57.10 (0.00-150.00)	28.60 (0.00-100.00)	**0.000**
Daily nuts (g) (median, min-max)	7.50 (0.00-57.10)	4.15 (0.00-41.40)	0.230
Daily legumes (g) (median, min-max)	15.00 (0.00-47.10)	10.00 (0.00-42.80)	0.163
Daily bread (g) (median, min-max)	193.75 (10.70-500.00)	150.00 (3.30-300.00)	0.130
Daily rice-pasta (g) (median, min-max)	100.00 (20.00-342.90)	54.30 (0.00-180.00)	**0.000**
Daily vegetable (g) (median, min-max)	128.60 (0.00-385.70)	126.45 (31.40-368.70)	0.202
Daily fruit (g) (median, min-max)	117.85 (0.00-585.70)	114.30 (0.00-500.00)	0.954
Daily fast food (g) (median, min-max)	21.40 (0.00-114.30)	14.00 (0.00-100.00)	0.672
Daily energy intake (kkal) (median, min-max)	1960.00 (1360.70-2681.00)	1844.45 (1326.90-2681.00)	0.152
Daily carbohydrate (g) (median, min-max)	241.15 (172.10-386.40)	216.85 (151.20-386.40)	0.099
Daily protein (g) (mean±SD)	82.63±19.38	65.50±10.73	**0.000**
Daily fat (g) (mean±SD)	83.22±18.89	76.59±13.43	**0.029**
Daily fibre (g) (mean±SD)	21.01±7.42	19.70±5.03	0.260
Daily cholesterol (mg) (mean±SD)	313.40±117.38	265.42±94.86	**0.015**

g: gram, mg: milligram, SD: Standard derivation

milk-yoghurt, daily egg, daily rice-pasta, and daily protein intake are independent risk factors (p=0.020, p=0.003, p=0.006, p=0.001, respectively) (Table 3).

Table 3: Multivariate regression analysis of variables

	OR	95% CI	p value
Monthly income	0.844	0.217-3.285	0.080
Daily protein	0.899	0.841-0.959	**0.001**
Daily fat	1.037	0.994-1.082	0.097
Daily cholesterol	1.009	1.000-1.018	0.054
Daily milk-yoghurt	0.990	0.981-0.998	**0.020**
Daily red meat	1.013	0.968-1.060	0.569
Daily chicken	0.973	0.946-1.001	0.058
Daily salami-sausage	0.961	0.910-1.015	0.154
Daily egg	0.963	0.940-0.987	**0.003**
Daily rice-pasta	0.976	0.959-0.993	**0.006**

DISCUSSION

Gallstones are the leading cause of pancreatitis. The role of diet in the formation of gallbladder stones is an undeniable fact. There are many studies in the related literature.

Many studies have reported that eggs, red meat, animal fat, animal protein, and dietary cholesterol increase the cholesterol content in bile and increase cholesterol gallstones (14-16). It has been reported in some studies that high-protein diets prevent gallstone formation (17,18). Previous studies have shown that refined sugar, cakes and cakes, and beverages containing sucrose increase the risk of gallstones (19,20).

Low consumption of vegetables and high consumption of fat and meat may contribute to the aetiology and development of AP. The secretion of cholecystokinin is increased when meat or fat is consumed by stimulating

the pancreas. The inflammatory cascade may also be influenced by dietary components that have a role in AP pathogenesis by causing reactive oxygen and nitrogen species (21). The pancreas can be sensitive to oxidative stress if its antioxidant status is imbalanced because of dietary factors. In a study that evaluated the relationship between pancreatitis severity and diet and included patients with AP which developed due to many etiological factors, it was stated that increased meat consumption was an independent risk factor for increased pancreatitis severity (22).

In a study by Setiawan et al. that evaluated the relationship between pancreatitis and diet between 1993 and 1996, a positive relationship was found between red meat consumption and AP due to gallstones. In addition, a relationship was found between the consumption of eggs, saturated fatty acids, and cholesterol and the development of AP due to gallstones. On the contrary, it has been observed that there is a negative relationship between pancreatitis and dietary fibre intake, fruit consumption, and the amount of milk consumed. However, in this study, pancreatitis patients were evaluated among themselves according to their consumption frequency, and it was not evaluated whether it affected the development of ABP (23). A large cross-sectional study from China had a positive association with the risk of acute pancreatitis in a high-meat diet model (24).

There is an increased risk for AP associated with overall and saturated fat intake, but no effect of fibre intake on pancreatitis according to the Iowa Women's Health Study (25). Acute pancreatitis appears to be caused by a combination of gallstones and a prolonged high-fat diet, suggesting diet might play a role as a cofactor in AP's onset, according to a previous systematic review (26). An increased risk of ABP has also been linked to a high-cholesterol diet according to two studies. There is a strong connection between high-fat and cholesterol diets and the development of gallstones, both in animal and human studies (27,28).

Wilson et al. in their study in 1985 evaluated patients with acute pancreatitis due to gallstones and patients who did not develop pancreatitis despite having stones in the common bile duct in terms of daily protein, fat, and carbohydrate intake, and there was no significant difference between the groups (6).

In our study, similar to some studies in the literature, daily protein, red meat, egg, fat, and cholesterol consumption is significantly higher in patients with gallbladder pancreatitis. Although there are publications in the literature suggesting that there is an inverse relationship between fibre intake and milk use and AP, there are also publications that do not show any correlation. In our study, no relationship was found between the development of AP and fibre intake, but a positive relationship was observed between the intake of milk-yoghurt and the development of AP. The relationship between the intake of milk-yoghurt and AP can be explained by the preference for fatty milk and yoghurts in our society. In our study, pancreatitis was observed more frequently in patients with gallstones with a higher monthly income, which can probably be explained by easier access to meat, milk, eggs, etc.

Although there are studies showing that fish consumption protects against pancreatitis not related to the gallbladder, no association was found between fish consumption and pancreatitis risk in other multi-ethnic studies (29). In the same study, an inverse relationship was reported between fish consumption and gallbladder acute pancreatitis in the Caucasian population (23). In our study, no significant difference was observed between groups in terms of fish consumption.

Acute pancreatitis is reported to be associated with smoking (30,31). There is a two fold increase in the risk of non-gallstone-related AP among smokers, but not for gallstone-related AP, according to a Swedish study (31). In our study, no difference was found in smoking rates in patients with AP compared to those with only gallstones.

There are very few studies in the literature evaluating the relationship between rice-pasta consumption and AP. Although a positive correlation was reported between parboiled rice and AP in one of these studies, it is not known whether the cases were related to AP due to gallstones (11). In our study, a positive relationship was found between the consumption of rice-pasta and AP due to gallstones. We think that this is not related to the intake of rice or pasta, but to the intake of a large amount of oil during the cooking of these dishes in our country.

Limitations of this study: the limited number of patients, the history of the patients could not be standardized, and situations that may arise from cultural differences could not be evaluated.

CONCLUSIONS

As a result, our study sought to answer which foods may cause pancreatitis in individuals with gallstones, which have been evaluated in very few articles in the literature, and it may be that the intake of red meat, eggs, fat, cholesterol, and protein, which are thought to play a role in the aetiology of AP, may be important in the development of AP related to gallbladder stones. Although an inverse relationship has been reported between the development of AP and the intake of fibre and milk, especially in the literature, a positive relationship was found between the development of AP and these products in our study, especially due to increased fat intake in milk and rice-pasta products. Paying attention to the consumption of these foods can give satisfactory results in preventing

the development of AP in people with gallstones.

Ethics Committee Approval: This study was approved by Istanbul Training and Research Hospital Clinical Research Ethics Committee (Date: 02.10.2020, No: 2530).

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ASSESSMENT OF THE RANSON SCORE IN ACUTE PANCREATITIS: ITS VALUE IN AN EMERGENCY SETTING UPON ADMISSION

AKUT PANKREATİTTE RANSON SKORUNUN DEĞERLENDİRİLMESİ: ACİL SERVİSE BAŞVURU ANINDA DEĞERİ

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ABSTRACT

Objective: Ranson criteria, introduced in 1974, was the first clinical prediction rule for acute pancreatitis in which five admission parameters and six (or five) late components collected within 48 hours were used to reach a clinical decision. This 48-hour follow-up requirement was not convenient for use in the emergency department setting. This study was undertaken to assess whether five admission Ranson parameters may have use in differentiating edematous pancreatitis from necrotizing pancreatitis in the emergency department setting.

Material and Method: Patient data for this retrospective cohort study was gathered from 205 patients treated for acute pancreatitis from January 2018 to December 2022 in a tertiary care center. The patient files were extracted from the archives for clinical data gathering. Laboratory admission data and radiology reports were extracted from the automated laboratory reporting system.

Result: The 205 acute pancreatitis patients were mostly female and in their sixth decade. The etiology was mostly biliary pancreatitis (76%). Patient history revealed that 80% was the first attack. The radiologic imaging study review revealed the majority of the patients had edematous pancreatitis (87%). Higher scores in admission Ranson score (aRS) weakly predicted increasingly higher probability (2.6% for aRS 0 to 28.6% for aRS 4-5) for the presence of necrosis without reaching statistical significance (p=0.055). When components of the score were analyzed, age, LDH levels, and glucose had no discriminating value, WBC parameter positi-

ÖZET

Amaç: 1974'te tanımlanan Ranson kriterleri, klinik bir karara varmak için 48 saat içinde toplanan 5 kabul parametresi ve 6 (veya 5) geç bileşenin kullanıldığı akut pankreatit için ilk klinik tahmin kuralıydı. Bu 48 saatlik takip gerekliliği, Acil Servis ortamında kullanım için uygun değildi. Bu çalışma, acil servis ortamında ödematöz pankreatitin nekrotizan pankreatitten ayırt edilmesinde 5 kabul Ranson parametresinin kullanılıp kullanılamayacağını değerlendirmek için yapılmıştır.

Gereç ve Yöntem: Bu retrospektif kohort çalışması için hasta verileri, üçüncü basamak bir bakım merkezinde Ocak 2018 ile Aralık 2022 arasında akut pankreatit nedeniyle tedavi edilen 205 hastadan toplandı. Hasta dosyaları, klinik veri toplamak için arşivlerden çıkarıldı. Laboratuvar kabul verileri ve radyoloji raporları otomatik laboratuvar raporlama sisteminden alınmıştır.

Bulgular: İki yüz beş akut pankreatit hastasının çoğu kadındı ve altıncı dekattaydı. Etiyoloji çoğunlukla biliyer pankreatit (%76) idi. Hasta öyküsü, %80'inin ilk atak olduğunu ortaya koydu. Radyolojik görüntüleme çalışması incelemesi, hastaların çoğunda (%87) ödematöz pankreatit olduğunu ortaya çıkardı. Başvurudaki daha yüksek Ranson skoru (aRS), istatistiksel anlamlılığa ulaşmadan (p=0.055) nekroz varlığı için daha yüksek bir olasılığı (aRS 0 için %2.6 ila aRS 4-5 için %28.6) zayıf şekilde öngördü. Skorun bileşenleri analiz edildiğinde, yaş, LDH düzeyleri ve glukozun ayırt edici bir değeri yoktu, WBC parametresinin pozitifliği nekrotizan pankreatit olasılığını önemli ölçüde artırırken, pozitif AST düzeyi nekrotizan pankreatit riskini önemli ölçüde azalttı.

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tivity significantly increased the odds of necrotizing pancreatitis, whereas positive AST level significantly decreased the risk of necrotizing pancreatitis.

Conclusion: In conclusion, aRS had little utility in predicting pancreatic necrosis.

Keywords: Ranson score, acute pancreatitis, necrotizing pancreatitis, edematous pancreatitis

Sonuç: Sonuç olarak, aRS'nin pankreas nekrozunu tahmin etmede çok az faydası vardı.

Anahtar Kelimeler: Ranson skoru, akut pankreatit, nekrotizan pankreatit, ödematöz pankreatit

INTRODUCTION

Acute pancreatitis is an acute inflammatory disease of the pancreas. It typically manifests as excruciating abdominal discomfort, may influence several organ systems, and can result in organ dysfunction. According to the Atlanta classification, the two major subtypes are interstitial edematous and necrotizing acute pancreatitis (1). Although it has a one to five percent overall mortality rate, pancreatic necrosis can increase that number to 15% (2,3).

Ranson criteria were introduced by Dr. John Ranson in 1974 as a clinical prediction rule for forecasting the severity and the risk of mortality of an acute pancreatitis episode (4). As conceived, the criteria had two separate components: the early component or data collected on admission which may basically predict the risk of pancreatic necrosis, and the late component collected 48 hours later which deals with other complications that may arise from severe acute pancreatitis such as third space sequestration of volume, hemoconcentration, and pre-renal acute kidney injury, acidosis, hypocalcemia, and hypoxemia due to respiratory distress.

As the score can only give meaningful prognostic information after all the 11 components are collected, 48 hours must elapse before any prognostic information can be gleaned. As this state of affairs was deemed unacceptable, different scoring systems have been proposed with varying success among which Acute Physiology and Chronic Health Evaluation II (APACHE II) (5) and Bedside Index of Severity In Acute Pancreatitis (BISAP) (6) whose scores can be calculated at any time point were the most useful. But these scoring systems are cumbersome to use in an emergency department setting and are a statement about the critical state of the patient not whether the patient had necrotizing or edematous pancreatitis (7, 8). Therefore, the question was asked whether five easily obtained early Ranson score components can be used to predict the presence of pancreatic necrosis hence giving an idea of the disease severity.

This study was undertaken to assess whether the admission Ranson score may have use in differentiating edematous pancreatitis from necrotizing pancreatitis in the emergency department setting.

MATERIAL and METHODS

Study population

Patient data for this retrospective cohort study was gathered from 205 patients treated for acute pancreatitis from January 2018 to December 2022 in a tertiary care center; Istanbul University, Istanbul Faculty of Medicine, Emergency Internal Medicine Division. Patients who meet two of the following three criteria were included in the study: Acute onset of back-radiating epigastric pain, a threefold or higher increase in serum lipase or amylase above the upper limit of normal, and detection of pancreatitis on imaging. Patients with suspected diagnoses and missing data were excluded from the study. Ranson scoring was done separately according to biliary and non-biliary pancreatitis classification. Age: + if >70 years for biliary, >55 years for other causes of pancreatitis, WBC: White blood cells + if >18000 cells/mm^3 for biliary, >16000 cells/mm^3 for other causes of pancreatitis, LDH: + if >250 IU/l for biliary, >350 IU/l for other causes of pancreatitis, AST: + if >250 IU/l for biliary, >250 IU/l for other causes of pancreatitis, Glucose: + if >220 mg/dl for biliary, >200 mg/dl for other causes of pancreatitis (Table5).

Study protocol

The patient files were extracted from the archives for clinical data. Laboratory admission data was extracted from an automated laboratory reporting system and imaging data were reviewed from digital images stored in the same system. The study was conducted in accordance with the Declaration of Helsinki. The study was found ethically appropriate by the Ethics Committee of Istanbul University, Istanbul Medical Faculty (Date: 17.02.2023, No: 04).

Statistical analysis

Patient data were analyzed using SPSS for Windows version 28.0 (IBM Corp., Armonk, NY, U.S.A.). Numerical data were given as mean±standard deviation and categorical data as frequency and percent. Two group comparisons of numerical data with normal distribution were carried out using independent samples Student's t-test. If the numerical data had non-normal distribution, the Mann-Whitney U test was used. Categorical data comparison was carried out using the χ^2 test. If expected frequencies in cells were lower than five, groups were joined where appropriate un-

Table 1: Demographic data of the acute pancreatitis patients (n=205)

Variable	Value
Age (years)	56±17 (18–99)
Gender (n/%)	
Male	93 (45%)
Female	112 (55%)
Etiology (n/%)	
Biliary	155 (76%)
Alcohol	20 (10%)
Post ERCP	13 (6%)
Hypertriglyceridemia	9 (4%)
Autoimmune	4 (2%)
Other	4 (2%)
Admission Ranson Score* (n/%)	
0	38 (18%)
1	79 (39%)
2	57 (28%)
3	21 (12%)
≥4	6 (3%)
Type (n/%)	
Edematous	179 (87%)
Necrotizing	26 (13%)
Chronicity (n/%)	
Acute	164 (80%)
Acute on chronic (recurrent)	41 (20%)

ERCP, Endoscopic retrograde cholangiopancreatography: Other, Malignancy (2), Medication (1), Genetic (1): * These are admission data of Ranson score, age, glucose level, AST level, LDH level, and WBC count.

Table 2: Admission hematologic and biochemical parameters of acute pancreatitis patients (n=205)

	Mean±SD€ (minimum-maximum)
Hematologic variables	
Hemoglobin (g/dl)	12.8±2.0 (7.5-17.9)
Hematocrit (%)	38±6 (24 -54)
MCV (fl)	85±7 (59-100)
RDW	15±2 (12-24)
WBC (10^3/ml)	11.3±5.3 (3.8-35)
Neutrophil count (10^3/ml)	9.0±5.2 (2-33)
Lymphocyte count (10^3/ml)	1.5±1.0 (0.3-11.5)
Platelet count (10^3/ml)	262±132 (10.5-1646)
Biochemical variables	
Glucose (mg/dl)	141±64 (64-651)
Creatinin (mg/dl)	1.0±0.7 (0.2-6.5)
Amylase (IU/l)	1305±1533 (23-7782)
Lipase (IU/l)	2784±3727 (13-21324)
AST (IU/l)	169±203 (9-1048)
LDH (IU/l)	356±172 (119-1415)
Total bilirubin (mg/dl)	2.1±2.5 (0.1-17.9)
Calcium (mg/dl) (n=165)	9.3±0.7 (6.4-12.3)
Albumin (g/dl)	4.0±0.6 (2.2-5.1)
Triglyceride (mg/dl) (n=93)	384±773 (45-4028)
CRP mg/l	57±97 (1-600)
INR	1.0±0.3 (0.8-4.1)
Urine amylase (IU/l) (n=95)	10556±23615 (31-151460)
Blood gases variables (n=150)	
pH	7.39±0.05 (7.23-7.60)
Lactate (mmol/l)	1.9±1.0 (0.5-8.8)

€: Standard deviation, MCV: Mean corpuscular volume, RDW: Red cell distribution width, WBC: White blood cell

til expected cell counts exceeded five. For 2*2 contingency tables, Yates correction was done. If assumptions were violated for 2*2 tables, Fisher's exact test was used.

RESULTS

The demographic data of the 205 acute pancreatitis patients are given in Table 1. Patients were mostly in their sixth decade with female preponderance. The etiology was overwhelmingly biliary (76%), and alcohol, post-ERCP, and hypertriglyceridemia were the cause in another 20%. Patient history revealed that 80% was the first attack, the rest having recurrent acute pancreatitis or chronic pancreatic disease. The radiologic imaging study review revealed the majority of the patients had edematous pancreatitis (87%) and only 13% of the cohort had necrosis. When the admission Ranson score was calculated from the five parameters: age, glucose, AST, LDH, and WBC count, approximately two-thirds of the patients had a score of 1 or 2, and 18% had a score of 0. Females had slightly higher scores compared to males (1.5±1.1 vs 1.3±0.9) without reaching statistical significance (p=0.111). Necrotizing pancreatitis was more frequent in males (16%) compared to females (10%) without reaching statistical significance (p=0.167).

Admission biochemical parameters are given in Table 2. Serum amylase and lipase and urine amylase levels are high as expected. Most of the biochemical parameters gathered, i.e., glucose, AST, LDH, bilirubin, and CRP levels, were all high with non-normal distribution.

Biochemical parameters were compared in edematous versus necrotizing pancreatitis and the results are shown in Table 3. There was no statistically significant difference for hematologic parameters except a difference in red cell distribution width (RDW) (p=0.036) which was not deemed clinically significant. Amylase and lipase levels were significantly lower in necrotic pancreatitis. Likewise, AST and total bilirubin levels were lower in necrotic pancreatitis (p=0.002, p=0.02 respectively). However, serum albumin levels were significantly lower (p=0.003) and CRP levels were significantly higher in the necrotic pancreatitis group (p<0.001).

Admission Ranson scores were compared in edematous and necrotizing pancreatitis groups (Table 4). Higher

Table 3: The comparison of biochemical parameters in edematous versus necrotizing pancreatitis

Variables	Type of pancreatitis		P value
	Edematous (n=178)	Necrotizing(n=26)	
Age (Years)	56±18	54±14	0.544
Hemoglobin (g/dl)	12.9±1.9	12.5±2.2	0.345
Hematocrit (%)	38±6	37±6	0.246
MCV (fl)	85±7	83±8	0.211
RDW	15±2	15±2	**0.036**
Platelet count (10^3/ml)	252±78	332±303	0.453
WBC count (10^3/ml)	10.8±4.5	14.5±8.3	0.053
Neutrophil count (10^3/ml)	8.6±4.3	12.3±8.4	0.052
Lymphocyte count (10^3/ml)	1.5±1.1	1.4±0.7	0.969
Glucose (mg/dl)	137±52	168±115	0.137
Amylase (IU/l)	1400±1564	653±1167	**0.002***
Lipase (IU/l)	3000±3806	1385±2866	**0.001***
Creatinine (mg/dl)	0.9±0.6	1.0±0.7	0.924
AST (IU/l)	185±211	69±76	**0.002***
LDH (IU/l)	356±177	365±142	0.809
Total bilirubin (mg/dl)	2.2±2.5	1.2±2.1	**0.02***
Albumin (g/dl)	4.1±0.6	3.6±0.7	**0.003***
Calcium (mg/dl)	9.3±0.7	9.0±0.8	0.059
CRP (mg/l)	45±79	138±159	<**0.001***
Triglycerides (mg/dl)	375±805	433±664	0.780
pH	7.39±0.05	7.40±0.06	0.339
Lactate (mmol/l)	1.9±1.1	2.2±1.1	0.099
INR	1.0±0.3	1.0±0.1	0.983

MCV: Mean corpuscular volume, RDW: Red cell distribution width, WBC: White blood cell, *: Mann-Whitney U test 2-sided significance

Table 4: Admission Ranson score in edematous versus necrotizing pancreatitis (n=205)

Ranson Score*	Type of pancreatitis		Total
	Edematous (n=178)	Necrotizing (n=26)	
0	37	1	38
1	68	11	79
2	50	7	57
3	19	5	24
≥4	5	2	7

*: Fisher's Exact test two-sided p= 0.055 (Ranson score 0 versus 1 or higher)

scores in admission Ranson score weakly predicted an increasingly higher probability for the presence of necrosis without reaching statistical significance. Admission Ranson scores of 0, 1, 2, 3, and 4 and above are associated with 2.6%, 14.1%, 12.3%, 20.8%, and 28.6% possibility of necrotic pancreatitis respectively with the pre-test probability being 13% in necrotizing pancreatitis.

Components of the admission Ranson score were compared for edematous and necrotizing pancreatitis cases for their discrimination value (Table 5). Age, LDH levels, and glucose had no discriminating value. White blood cell count Ranson parameter positivity increased 5-fold the odds of necrotizing pancreatitis, whereas a positive AST level Ranson parameter significantly decreased the risk of necrotizing pancreatitis.

DISCUSSION

Foreknowledge about the course of a disease in a patient has preoccupied the medical profession from the times of Hippocrates (9). For acute pancreatitis, Ranson

Table 5: Significance of the elements of admission Ranson score for differentiating edematous from necrotic pancreatitis

Admission Ranson score parameters	Type of pancreatitis		Odds Ratio (95% CI)	P value
	Edematous	Necrotic		
Age (years)			1.99 (0.85-4.62)	0.107
-	130	15		
+	48	11		
WBC (10^3/ml)			5.36 (2.06-13.96)	**0.001**
-	162	17		
+	16	9		
LDH (IU/l)			0.77 (0.33-1.82)	0.550
-	59	10		
+	115	15		
AST (IU/l)			0.12 (0.02-0.89)	**0.014**
-	129	21		
+	46	1		
Glucose (mg/dl)			2.79 (0.91-8.53)	0.074
-	164	21		
+	14	5		

WBC: White blood cell, LDH: Lactate dehydrogenase AST: Aspartate aminotransferase. The classification is explained in the material and method

criteria were the first to be proposed (4). It was geared towards acute pancreatitis patients admitted to a surgical ward, and during the follow-up of 48 hours, the surgeon used this clinical decision rule to assess whether operative treatment was required (10). As this leisurely state of affairs does not address the concerns of an emergency department, at least 17 other clinical decision rules have been validated (11). However, the Holy Grail of emergency decision rules, one that is simple and easy to implement and straightforward to interpret is still to be validated (12).

Ranson criteria have several issues which make it less than ideal for evaluation in the Emergency department. First, it seems that an APACHE II score >7 or BISAP score >2 has higher sensitivity and specificity in predicting severe acute pancreatitis (13, 14). Second, the leisurely 48-hour observation period needed in Ranson criteria, a time that Emergency Departments do not have, makes the criteria ineffectual. However, this is not an issue for either APACHE II or BISAP scores which may be implemented repeatedly at any time after admission. The APACHE II score was developed for patients in Intensive Care Unit and may be difficult to use in an Emergency Department, but the BISAP score is a bedside scoring system and should be easier to implement, though the SIRS component requires four additional parameters (8). Third, Ranson Criteria validity for patients aged less than 30 years, or in patients living in higher altitudes is less than certain (15, 16). Fourth, the fact that there are 11 components in the Ranson criteria may make the assessment process cumbersome for clinicians.

It was tempting to use the admission Ranson criteria to predict pancreatic necrosis. The elements of the score were hypothesized to be directed towards showing pancreatic inflammation (WBC), specific (glucose), and nonspecific (AST, LDH) pancreatic cellular injury and were easy to gather. However, only increased WBC count was significantly related to pancreatic necrosis. Surprisingly, AST level increase was associated with edematous pancreatitis, not necrosis. A recent reassessment of the Ranson score in 938 acute pancreatitis patients, excluding AST from calculations, caused a better fit to the data in predicting severe pancreatitis, which puts the utility of AST in the prediction scheme in doubt (17).

In conclusion, there is no easy method for predicting the severity of acute pancreatitis or detecting pancreatic necrosis at the bedside, and admission Ranson criteria were of little utility.

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ABSENCE OF FOVEAL DEPRESSION AND ITS ASSOCIATION WITH REFRACTIVE STATUS AND STRABISMUS IN CHILDREN WITH HISTORY OF RETINOPATHY OF PREMATURITY

PREMATÜRE RETİNOPATİSİ ÖYKÜSÜ OLAN ÇOCUKLARDA FOVEAL DEPRESYON YOKLUĞUNUN REFRAKTİF KUSURLAR VE ŞAŞILIK İLE İLİŞKİSİ

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ABSTRACT

Objective: To evaluate the foveal depression (FD) status on optical coherence tomography (OCT) and its relationship with strabismus, amblyopia and refractive errors in children with a history of retinopathy of prematurity (ROP).

Material and Method: Medical records were reviewed for demographic data, ocular and medical history, systemic disorders, ophthalmologic and OCT findings. Patients were categorized into two groups according to foveal depression status on OCT: absence of FD (Non-FD Group) and presence of FD (FD Group). Demographic data, refractive errors (RE), strabismus, amblyopia and anisometropia were compared between the groups.

Result: Mean age of the patients was 11.1±2.7 years in the Non-FD group and 10.1±2.9 years in the FD group (p=0.136). Mean gestational age (GA) at birth and birth weight (BW) of the Non-FD group (28.8±2.7 weeks, 1269.1±455.5 grams) were significantly lower than those of the FD group (30.8±2.1weeks, 1530.8±415.2 grams) (p=0.002 and p=0.02, respectively). Although there was no significant difference between the groups in the mean spherical equivalent (SE) RE (-1.19± 4.86D in the Non-FD group and 0.77±4.08D in the FD group, p=0.09), the distribution of SE refractive errors was significantly different (p=0.001). 54.5% of patients in the Non-FD group had myopia and 72% of the patients in the FD group had hypermetropia. Mild myopia was significantly more in the Non-FD group and mild hypermetropia was significantly more in the FD group (p<0.05 for both). Astigmatism equal or greater than 1.50D was detected in

ÖZET

Amaç: Prematüre retinopatisi (ROP) öyküsü olan çocuklarda optik koherens tomografide (OKT) foveal depresyon (FD) durumunu ve şaşılık, ambliyopi ve refraktif kusurlar ile ilişkisini değerlendirmek.

Gereç ve Yöntem: ROP öyküsü olan hastaların klinik kayıtlarından; demografik veriler, oküler ve medikal öykü, sistemik hastalıklar, oftalmolojik ve OKT bulguları incelendi. Hastalar OKT'de FD durumuna göre iki gruba ayrıldı: FD yokluğu (Non-FD Grup) ve FD varlığı (FD Grup). Demografik veriler, refraktif kusurlar, şaşılık, ambliyopi ve anizometropi iki grup arasında kaşılaştırıldı.

Bulgular: Hastaların ortalama yaşı; Non-FD grupta 11,1±2,7 yıl, FD grupta 10,1±2,9 yıl idi (p=0,136). Ortalama doğum haftası (DH) ve doğum ağırlığı (DA) Non-FD grupta (28,8±2,7 hafta, 1269,1±455,5 gram) FD gruba göre (30,8±2,1 hafta,1530,8±415,2 gram) anlamlı olarak daha düşüktü (p=0,002, p=0,02). Ortalama sferik ekivalan (SE) refraktif kusurlar gruplar arasında anlamlı farklılık göstermemekle birlikte (Non-FD grupta -1,19±4,86D, FD grupta 0,77±4,08D, p=0,09), SE refraktif kusurların dağılımı anlamlı olarak farklıydı (p=0,001). Non-FD grubun %54,5'inde miyopi, FD grubun %72'sinde hipermetropi mevcuttu. Hafif miyopi Non-FD grupta, hafif hipermetropi FD grup'ta daha fazla saptandı (p<0,05). Non-FD grubun %56,5'inde, FD grubun %36'sında 1,50D ve üzeri astigmatizma mevcuttu (p>0,05). Şaşılık, ambliyopi ve anizometropi insidasında gruplar arasında anlamlı fark saptanmadı (p>0,05).

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56.5% of the Non-FD group and 36% of the FD group (p>0.05). There was no significant difference between the groups in the incidence of strabismus, amblyopia and anisometropia (p>0.05).

Conclusion: We detected lower GA and BW in the Non-FD group than those of the FD group. Myopia is more prevalent in patients with a history of ROP and absence of FD than in those with a normal foveal structure.

Keywords: Retinopathy of prematurity, optical coherence tomography, myopia, astigmatism, strabismus, refractive errors

Sonuç: FD yokluğu olan hastalarda daha düşük doğum haftası ve doğum ağırlığı saptanmıştır. ROP öyküsü olan hastalarda FD yokluğu eşlik etmesi durumunda, normal foveal yapı gösterenlere göre daha sık miyopi izlenmiştir.

Anahtar Kelimeler: Prematüre retinopatisi, optik koherens tomografi, şaşılık, refraktif bozukluk

INTRODUCTION

Long-term ophthalmologic pathologies associated with retinopathy of prematurity (ROP) have been more prevalent with improvement in neonatal care. The ROP associated ocular pathologies are strabismus, amblyopia, refractive errors, retinal detachment, cataracts and glaucoma (1-3). In recent years, the development of imaging technology has allowed the foveal structure to be evaluated in detail, and structural abnormalities such as foveal dysplasia and absence of foveal depression (FD) can be detected in patients with a history of ROP (4-7). Absence of FD has also been reported in healthy children and children without a history of ROP (6).

In previous studies, optical coherence tomography (OCT) findings were evaluated according to ROP status and/or ROP treatment. The aim of this study is to evaluate the FD status on OCT and its relationship with strabismus, amblyopia and refractive errors in children with a history of ROP.

MATERIAL and METHODS

The study was carried out retrospectively in the Department of Ophthalmology, Istanbul University, Istanbul Faculty of Medicine. Clinical records of 90 children with a history of ROP were reviewed for demographic data, medical history, systemic disorders, ocular and OCT findings. Ophthalmologic examination including best corrected Snellen visual acuity (BCVA), biomicroscopic and fundus evaluation, cycloplegic autorefraction and strabismus testing (Hirschberg, prism cover and/or Krimsky testing) was performed. Gestational age (GA) at birth, birth weight (BW), presence of ROP and treatment for ROP, BCVA, cycloplegic autorefraction and presence of strabismus, amblyopia and anisometropia were recorded.

For pupil dilation, 1% cyclopentolate was applied 3 times at 5-minute intervals. Cycloplegic autorefraction by an automatic keratorefractometer (ARK-530A, Nidek, Gamagori Aichi, Japan) was performed 30 minutes after the last drop was instilled. Visual acuity values obtained using the Snellen chart were converted to the logarithm of the minimum angle of resolution (logMAR).

Central macular thickness (CMT) and FD status were analyzed from OCT scans obtained with spectral-domain optical coherence tomography (SD-OCT) (Heidelberg Engineering, Heidelberg, Germany). Automated retinal thickness map was used in OCT analysis. The retinal thickness map consists of inner, middle, and outer rings with radii of 1 mm, 3 mm, and 6 mm, respectively, corresponding to the foveal, parafoveal, and perifoveal areas. CMT was defined as the mean thickness within the inner circle. FD was determined by subtracting CMT from mean parafoveal thickness. Values less than 56.4 µm were defined as an absence of FD as reported before (6).

All patients with systemic or neurologic disorders (hydrocephalus, epilepsy, cerebral palsy, mental-motor retardation), history of intraocular surgery and all eyes with abnormal retinal findings (retinal detachment, retinal traction, macular folds and dragging) and poor OCT image quality were excluded from the study. Patients were categorized into 2 groups: presence of FD (FD group) (Figure 1A), absence of FD (non-FD group) (Figure 1B). Spherical, cylindrical and spherical equivalent (SE) refractive errors were recorded for each eye. SE refractive errors were categorized into 3 groups: emmetropia (-0.74

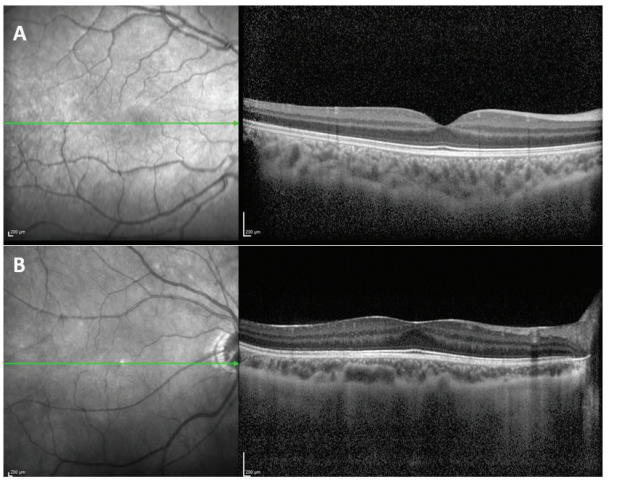

Figure 1: Optical coherence tomography images of the patients in foveal depression (FD) group (A) and non-foveal depression (non-FD) group (B)

diopters [D] to +0.74D), myopia (mild:-0.75D to -2.99D, moderate: -3.00D to -5.99D, high: -6D or more extreme), hypermetropia (mild: +0.75D to +2.99D, moderate: +3.00 D to +4.99D, high: +5.00D or more extreme). Astigmatism was categorized into 3 groups: mild (0.25 to 1.49D), moderate (1.5 to 2.99D) and high (3D or more extreme).

Ophthalmologic findings and OCT scans were recorded for both eyes of all patients.

One eye of each patient was randomly selected and included in the analysis.

The study adhered to the tenets of the Declaration of Helsinki and was approved by the Istanbul Faculty of Medicine Clinical Research Ethics Committee (Date: 27.05.2022, No: 10). Prior to treatment for ROP, patients' families or caregivers gave written informed consent.

A statistical software package (SPSS for Windows, v. 21.0, IBM Corp, ARMONK, NY: USA) was used for statistical analysis. Fischer's Exact test, Student's T-test, Mann-Whitney U test and Pearson Chi-Square test were performed to compare the numerical variables among 2 groups. Post-hoc analysis was used to evaluate the distribution of spherical refractive errors. Results of $p < 0.05$ were considered significant.

RESULTS

Seventy one patients (71 eyes) were included in the study. There were 46 patients in the Non-FD group and 25 patients in the FD group. Mean age of the patients at the last examination was 11.1±2.7 years in the Non-FD group and 10.1±2.9 years in the FD group (p=0.136). Mean GA and mean BW of the Non-FD group were significantly lower than those of the FD group (p=0.002 and p=0.02, respectively). There was no significant difference between the two groups in terms of gender distribution (p=0.08). Thirty-two patients (69.6%) in the Non-FD group and 12 patients (48%) in the FD had history of laser treatment for ROP (p=0.074). Of the patients who underwent laser treatment in the Non-FD group; 6 had zone 1 aggressive ROP, 4 had zone 2 stage 2 ROP with plus disease, 22 had zone 2 stage 3 ROP with plus disease.

All patients who underwent laser treatment in the FD group had zone 2 stage 3 ROP with plus disease. The demographic data of the patients in the groups are shown in Table 1.

At last examination, the mean logMAR BCVA of the patients was 0.14±0.17 LogMAR in the Non-FD group and 0.18±0.32 LogMAR in the FD group (p=0.467). Mean spherical equivalent (SE) refractive error of the patients was -1.19±4.86D in the Non-FD group and 0.77±4.08D in the FD group (p=0.09). 54.5% of the patients in the Non-FD group had myopia and 72% of the patients in the FD group had hypermetropia. Distribution of SE refractive errors was significantly different between two groups (p=0.001). Mild myopia was significantly more in the Non-FD group and mild hypermetropia was significantly more in the FD group ($p<0.05$ for both in post-hoc analysis). Strabismus was detected in 45.6% of patients in the Non-FD group and 44% of patients in the FD group (p=0.894). Esotropia was the most detected type of strabismus in both groups. There was no significant difference between the groups in terms of amblyopia and anisometropia (p=0.565 and p=0.562, respectively). Refractive errors, strabismus and amblyopia distributions of the groups are shown in Table 2.

Mean CMT of the patients was 312.5±31.1 µm in the Non-FD group and 272.8±24.4µm in the FD group ($p<0.001$). Mean foveal depression of the patients was 32.6±17.1µm in the Non-FD group and 70.5±11.9µm in the FD group ($p<0.001$).

When the patients who underwent laser treatment were compared, spherical equivalent refractive error distribution, mean CMT and foveal depression were found to be significantly different between the groups (p=0.043, p=0.001 and $p<0.001$, respectively). The demographic data, refractive errors, strabismus and amblyopia distributions of the patients who underwent laser treatment in

Table 1: Demographic data analysis of the groups

	Non-FD group (n=46)	FD group (n=25)	P values
Gestational age (weeks)	28.8±2.7	30.8±2.1	0.002[a]
Birth weight (grams)	1269.1±455.5	1530.8±415.2	0.020[a]
Gender			
Female, n (%)	20 (43.5)	16 (64)	0.080[b]
Male, n (%)	26 (56.5)	9 (36)	
Laser treatment, n (%)	32 (69.6)	12 (48)	0.074[c]
Laser treatment week	36.3±2.4	36.2±1	0.840[a]

FD: Foveal depression, [a]: Student t test, [b]: Fischer's exact test, [c]: Chi square test

Table 2: Refractive errors, strabismus and amblyopia distributions of two groups

	Non-FD group (n=46)	FD group (n=25)	P values
LogMAR BCVA (Snellen BCVA) (mean ± standard deviation)	0.14±0.17 (0.77±0.23)	0.18±0.32 (0.78±0.29)	0.467[a]
Spherical equivalent (SE) (D) (mean ± standard deviation)	-1.19±4.86	0.77±4.08	0.090[a]
Spherical refractive error (D)	-0.15±4.8	1.54±3.9	0.134[a]
Cylindrical refractive error (D)	-2.07±1.27	-1.50±1.1	0.065[a]
Emmetropia - total n (%) (-0.75D> SE <0.75D)	7 (15.2)	3 (12)	**0.001[b(*)]**
Myopia - total n (%) mild -0.75D ≥SE ≥ -2.99D** moderate -3.0D≥ SE≥-5.99D high -6.0D or more extreme	25 (54.4) **9** 9 7	4 (16) **0** 2 2	
Hypermetropia - total n (%) mild +0.75D≤ SE ≤ +2.99D** moderate +3.0D≤ SE ≤ +4.99D high +5.0D or more extreme	14 (30.4) **3** 9 2	18 (72) **12** 4 2	
Astigmatism - total n (%) no astigmatism mild 0.25 to1.49D moderate 1.5 to 2.99D high ≥3D	45 (97.8) 1 19 13 13	24 (96) 1 15 5 4	0.419[b]
Strabismus - total n (%) esotropia (ET) exotropia (XT) hypertropia hypotropia	21 (45.6) 13 8 1 (with XT) 0	11 (44) 8 3 1 (with ET) 0	0.894[b]
Anisometropia, n (%)	10 (21.7)	4 (16)	0.562[b]
Amblyopia, n (%)	14 (30.4)	6 (24)	0.565[b]

FD: Foveal depression, BCVA: Best corrected visual acuity, logMAR: Logarithm of the minimum angle of resolution, D: Diopter, a: Student t test , b: Chi Square test, *:The distribution of spherical refractive errors is significantly different among the groups. **: Group 1 vs group 2, p <0.05 in post-hoc analysis.

2 groups are shown in Table 3. Of six patients with zone 1 aggressive ROP in the Non-FD group; high myopia in 2, moderate myopia in 1, high hypermetropia in 1 and low hypermetropia in 2 were detected. High astigmatism was found in 2 patients, moderate in 1 patient, and low in 3 patients. Of these patients, 2 had amblyopia, 2 had anisometropia and 2 had strabismus.

DISCUSSION

In the present study, we aimed to evaluate the FD status on OCT and its relationship with strabismus, amblyopia and refractive errors in children with a history of ROP.

A previous histological study demonstrated that foveal pit formation begins at approximately at 25 weeks gestational age, it becomes wider and shallower after birth and appears mature by 15 months (8). Absence of FD, a type of abnormal foveal morphology, has been reported in aniridia, albinism, nanophthalmos, regressed ROP and also in preterm and healthy children (4-6, 9-14). Wu et al. suggested that normal development of fovea is affected in preterm infants and laser treatment/cryotherapy may have an additional effect on these changes by destroying avascular retina (6). In their study, patients treated for ROP had not only thicker maculas, but also lower GA and BW than untreated patients. A previous study evaluating preterm children suggested that the degree of prematurity is more important for foveal development than ROP (15). In our study, the mean GA and BW was significantly lower in the Non-FD group than in the FD group. On the other hand, when only the patients who underwent laser treatment were compared, the mean GA and BW were slightly lower in the Non-FD group, but the difference between the two groups was not statistically significant. In our study, consistent with the study by Akerblom

Table 3: Demographic data, refractive errors, strabismus and amblyopia distribution of patients with laser treatment in two groups

	Only laser treatment in Non-FD group (n=32)	Only laser treatment in FD group (n=12)	P values
Birth weight (grams)	1184.4±436	1409.2±435	0.097[a]
Gestational age (weeks)	28.5±2.7	29.7±1.5	0.117[a]
Mean central macular thickness	322.4±30.4	285.7±26.4	**0.001**[a]
Mean foveal depression	28.8±17.2	64.2±7.1	**<0.001**[a]
Anisometropia, n (%)	9 (28.1)	3 (25)	0.579[b]
Amblyopia, n (%)	13 (40.6)	3 (25)	0.276[b]
Strabismus - total n (%) esotropia (ET) exotropia (XT)	9 (28.1) 6 3	3 (25) 1 2	0.579[b]
LogMAR BCVA (mean ± standard deviation)	0.17±0.17	0.25±0.36	0.979[a]
Spherical equivalent (SE) (D) (mean ± standard deviation)	-2.38±4.82	-0.80±5.14	0.225[a]
Spherical refractive error (D)	-1.27±4.72	0.25±4.89	0.225[a]
Cylindrical refractive error (D)	-2.20±1.32	-2.02±1.14	0.721[a]
Astigmatism - total n (%)	32 (100)	12 (100)	0.942[c]
mild 0.25 to1.49D moderate 1.5 to 2.99D high ≥3D	14 9 9	5 4 3	
Emmetropia - total n (%) (-0.75D> SE <0.75D)	3 (9.3)	2 (16.7)	**0.043**[c]
Myopia - total n (%) mild -0.75D ≥SE ≥ -2.99D[a] moderate -3.0D≥ SE≥-5.99D high -6.0D or more extreme	22 (68.8) 7 9 6	3 (25) 0 1 2	
Hypermetropia - total n (%) mild +0.75D≥ SE ≥ +2.99D[b] moderate +3.0D≥ SE ≥ +4.99D high +5.0D or more extreme	7 (21.9) 2 5 0	7 (58.3) 5 2 0	

FD:foveal depression, BCVA: best corrected visual acuity, logMAR: logarithm of the minimum angle of resolution, D:diopter
[a]: Mann-Whitney U Test [b]: Fisher exact test, [c]: Chi Square test

et al, the degree of prematurity seems to have a greater effect on foveal development, but additional factors other than ROP and/or laser treatment may play a role in abnormal foveal development (15).

Previous studies demonstrated that absence of FD is not correlated with visual acuity in patients with a history of ROP (4,5). It has been suggested that photoreceptor maturation may have more impact than inner retinal layer migration on visual acuity (16). In our study, visual acuity did not differ significantly between the presence and absence of FD in the groups, which was consistent with previous studies.

Refractive status of patients with history of prematurity and/or ROP were evaluated in previous studies and the results were variable. It has been shown that there is no relationship between myopia and GA or BW in preterm children without ROP (17,18). It has been suggested that myopic refractive errors were frequently detected in children with history of ROP and/or ablative treatment (laser/cryotherapy) (6,19,20). Mild myopia has also been reported in patients with spontaneously regressed ROP and in patients born prematurely and without ROP (6). On the other hand, Darlow et al. reported no significant difference in myopia between preterms with or without ROP and the control group (21). Moreover,

Wang et al.detected hyperopia in patients with history of spontaneously regressed ROP (20). Previous studies evaluated refractive errors and foveal structure according to the status of ROP. In our study, we compared refractive status of patients with history of ROP according to presence or absence of FD and we did not find a significant difference between the groups in the mean SE. When the refractive errors were evaluated categorically, we found that most of the patients with absence of FD were myopic (54.4%), and those with normal foveal structure were mostly hyperopic (72%). In addition, we found that statistical difference was maintained when only the patients who had laser treatment were compared. The most significant difference between the groups was detected in the mild myopia and mild hypermetropia categories. Therefore, myopia may be more prevalent in patients with ROP and absence of FD than in those with a normal foveal structure.

The incidence of astigmatism which was defined as equal or greater than 1.0D was reported as 42-52% in ROP children (23,24). Villegas et al reported that astigmatism ≥1.50D was detected in 45% of normal children with fovea plana (24). In our study, astigmatism ≥1.50D (moderate or high astigmatism) was detected in 56.5% of patients with absence of FD and 36% of patients with presence of FD. The incidence of astigmatism ≥1.50D in patients with ROP and absence of FD was slightly higher than previously reported in the literature, despite the lower limit of astigmatism was 1D in the literature. However, there was no significant difference between the groups.

The incidence of strabismus in premature infants has been reported as 22-46% in previous studies and strabismus rate was higher in preterms with severe ROP (25-27). In accordance with the literature, we found the incidence of strabismus to be 45% in the Non-FD group and 44% in the FD group, and esotropia was the most frequent type of strabismus in both groups.

The incidence of anisometropia in patients with regressed ROP varies from 14% to 48% according to severity of ROP (27). In accordance with the literature, we detected anisometropia in 21.7% of the patients in the Non-FD group and in 16% of the patients in the FD group.

The incidence of amblyopia was reported as 14.3% in patients with spontaneously regressed ROP and 20.8% in patients with treatment for ROP (28). In another study grouping the prematurely born children according to GA, the incidence of amblyopia reported as 32% in patients with GA lower than 28 weeks and 22% in patients with GA between 28-32 weeks (25). Consistent with the literature, we found the incidence of amblyopia to be 30% in the Non-FD group with a mean GA of 28 weeks and 24% in the FD group with a mean GA of 30 weeks. When only the patients who underwent laser treatment were evaluated, we found a slightly higher incidence of amblyopia (40%) in the Non-FD group compared to the literature, although there was no significant difference between the two groups. In the FD group, the incidence of amblyopia was found to be similar in those with and without laser treatment.

The limitations of this study are its relatively small sample size for both groups and its cross sectional and retrospective nature. This study only demonstrates the association between the absence of FD and refractive errors in patients with a history of ROP. Further studies are needed with a larger patient population and in different patient groups with the absence of FD.

CONCLUSION

We detected lower GA and BW in the Non-FD group than those of the FD group. The degree of prematurity seems to have an impact on foveal development in patients with a history of ROP.

Although the absence of foveal depression does not affect visual acuity, foveal morphology appears to be associated with refractive errors in children with a history of ROP. Similarly, normal foveal morphology is associated with hyperopia and abnormal foveal morphology is more frequently associated with myopia in patients undergoing laser treatment.

Ethics Committee Approval: This study was approved by Istanbul Faculty of Medicine Clinical Research Ethics Committee (Date: 27.05.2022, No: 10).

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A RARE CAUSE OF DYSPHAGIA THAT IS TREATABLE WITH SURGERY: A SINGLE-CENTER CASE SERIES OF FORESTIER'S DISEASE

DİSFAJİNİN CERRAHİ İLE TEDAVİ EDİLEBİLİR NADİR BİR SEBEBİ: FORESTİER HASTALIĞININ TEK MERKEZLİ VAKA SERİSİ

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ABSTRACT

Objective: Diffuse idiopathic skeletal hyperostosis (DISH), Forestier's disease, is a systemic disease characterized by the abnormal ossification and calcification of the paravertebral ligaments and muscles in front of the vertebral bodies. It rarely causes clinical symptoms but sometimes produces dysphagia. This study will evaluate the effectiveness of the anterior cervical approach in patients with Forestier's disease who suffer from dysphagia.

Material and Method: In this series, a retrospective analysis was performed on five patients referred to our clinic with dysphagia. Clinical, demographic, and surgical features were evaluated.

Result: All of the cases were male. Their mean age was 63.6 (range 56-69). The involved regions were C3-4; C2-3; C6-7; C3-7; C3-D3. All the patients who have dysphagia were treated via the anterolateral cervical approach. There were no neurological deficits or complaints postoperatively. All the patients stated that they benefited from surgery.

Conclusion: Osteophyte resection by an anterolateral cervical approach is a safe and effective treatment option for dysphagia in Forestier's disease.

Keywords: Cervical spine, diffuse idiopathic skeletal hyperostosis, dysphagia, osteophyte

ÖZET

Amaç: Difüz idiopatik iskelet hiperosteozu (DİİH), Forestier hastalığı, vertebra korpuslarının önündeki paravertebral ligaman ve kasların anormal kalsifikasyonu ile karakterize sistemik bir hastalıktır. Klinik semptomlara nadiren sebep olurlar ve bu semptomlar arasında disfaji bulunmaktadır.

Gereç ve Yöntem: Bu vaka serisinde, kliniğimizde disfaji ile prezente olan beş DİİH tanılı hasta retrospektif olarak incelenmiştir. Klinik, demografik ve cerrahi bilgiler hastane kayıtlarından elde edilerek değerlendirilmiştir.

Bulgular: Tüm vakalar erkek ve ortalama yaş 63,6 (56-69) yıldı. Etkilenen bölgelerin C3-4; C2-3; C6-7; C3-7; C3-D3 olduğu saptandı. Tüm vakalarda anterolateral servikal yaklaşım uygulandı. Postoperatif yeni şikayet ve nörolojik defisit ile karşılaşılmadı. Tüm hastalar disfaji şikayetlerinin ameliyattan sonra geriledikle-rini belirttiler.

Sonuç: Anterolateral servikal yaklaşım Forestier hastalığında vertebra korpus anteriorunda bulunan osteofit rezeksiyonunda uygun ve güvenli bir seçenektir.

Anahtar Kelimeler: Difüz idiopatik iskelet hiperosteozu, disfaji, osteofit, servikal vertebra

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INTRODUCTION

Diffuse idiopathic skeletal hyperostosis (DISH), a Forestier's disease, is a systemic disease characterized by the abnormal ossification and calcification of the paravertebral ligaments and muscles in front of the vertebral bodies. Forestier and Rotes-Querol first described the disease in 1950 (1,2).

The etiology is not well known. Ninety-seven percent of the cases occur in the thoracic spine, in the lumbar spine 90%, in the cervical spine 78%, and in all three segments 70%. Forestier's disease may be seen in all genders and races but usually in patients in their 60s (3). It rarely causes clinical symptoms but sometimes leads to dysphagia, pain, stiffness, reduced articular motion, and dysphonia (4–6).

Forestier's disease is managed conservatively. Surgical resection through the anterior approach provides resolution of the dysphagia (7). The study reports on five cases of dysphagia due to the osteophytes of the cervical levels.

MATERIAL and METHODS

Study design

In this series, a retrospective analysis was performed on patients with Forestier's disease referred to our clinic with dysphagia between 2005-2021. The minimum follow-up period was 12 months.

Patient population

This study included five patients who underwent anterolateral cervical resection of osteophytes to treat dysphagia caused by Forestier's disease. The diagnosis was made according to the criteria suggested by Resnick and Niwayama (8). All the patients exhibited dysphagia persisting for more than 12 months.

Radiological evaluation

In all the patients, lateral plain radiographs showed anterior osteophytes. All the patients were evaluated by X-rays, computerized tomography (CT) scanning, and magnetic resonance imaging (MRI) of the cervical and thoracic vertebrae.

Surgical technique

The patient is positioned with a shoulder support pillow enabling a 15 degree extension of the neck. Anteroposterior (AP) and lateral X-rays are used for determining the level and planning the incision. The incision is made longitudinal and parallel to the medial border of the sternocleidomastoid (SCM) muscle. The longitudinal incision allows a broader exposure of the cervical spine. After incising the platysma muscle, the medial border of the SCM muscle is determined and retracted laterally. Additional attention is paid to palpating the carotid artery and retracting it laterally under the SCM muscle. The esophagus is carefully dissected and retracted medially, avoiding any further compression. A marker is placed, and X-ray control of the levels is achieved. Once the correct levels are identified, and osteophytes are exposed, the high-speed drill is used to drill the osteophytes. Care should be taken not to disrupt the vertebral bodies and the annulus fibrosis. The lateral extent of the osteophytes can be removed. Bone bleeding is handled with bone wax. Soft tissues are spared through the procedure. After adequate decompression, a drain can be left in the surgical site. The wound is closed in layers.

Postoperative period and follow-up evaluation

On the first postoperative day, the patients were mobilized, and the drain was removed. Oral intake was begun in the 6th hour. As the symptoms resolved, the patient was put on a regular diet. A cervical collar was not required. Patients were evaluated in the outpatient clinic for one week, one month, six months, and one year after surgery. AP and lateral X-rays, CT scans, and MRI were obtained at each visit (Figure 1). This study was approved by Istanbul Faculty of Medicine Clinical Research Ethics Committee (Date: 03.02.2023, No: 03).

RESULTS

All of the cases were male, and the mean age was 63.6 (range 56-69). In the five patients included in the study, the involved regions were C3-4, C2-3, C6-7, C3-7, and C3-D3. All the patients who have dysphagia were treated via the anterolateral cervical approach. A longitudinal cervical incision along the SCM muscle allowed adequate pathology exposure even for more laterally extending osteophytes. The mean operation duration was 132 minutes (102-156). The surgery was feasible for all cases.

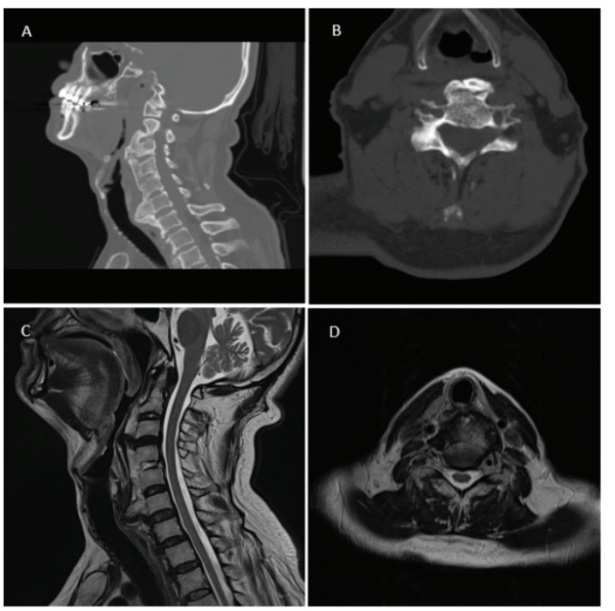

Figure 1: Preoperative CT (A, B) and MRI (C, D) scans of a patient with DISH presented with dysphagia

The total removal of the osteophytes was appreciated in postoperative imaging (Figures 2 and 3). There were no neurological deficits or complaints postoperatively. All the patients stated that they benefited from the surgery.

The minimum follow-up period was 12 months, with an average of 17 months. The patients tolerated the diet during their hospital stay. However, dysphagia resolved completely after two weeks. Complete removal of the osteophytes was seen in early postoperative radiographs. Radiographs at the first-year follow-up showed minimal regrowth of the osteophytes in all patients, but the patients had no symptoms. There were no instability findings.

DISCUSSION

DISH is a rare condition characterized by paravertebral ligament calcification and ossification in the anterior parts of the vertebral bodies. It may be seen in all genders, but the frequency is higher in males, and the incidence increases with age (9,10). It is more common in Mediterranean countries, especially Turkiye and Italy (11). The etiology is not known clearly. Mechanical factors such as the proximity of the aorta causing bony bridging, genetic factors, environmental exposures like fluoride and retinol, and drugs like vitamin A derivatives are some of the culprits (12). Recent studies also discovered the correlation between Forestier's disease and various metabolic disorders such as obesity, hyperlipidemia, hyperinsulinemia, and hypertension (13).

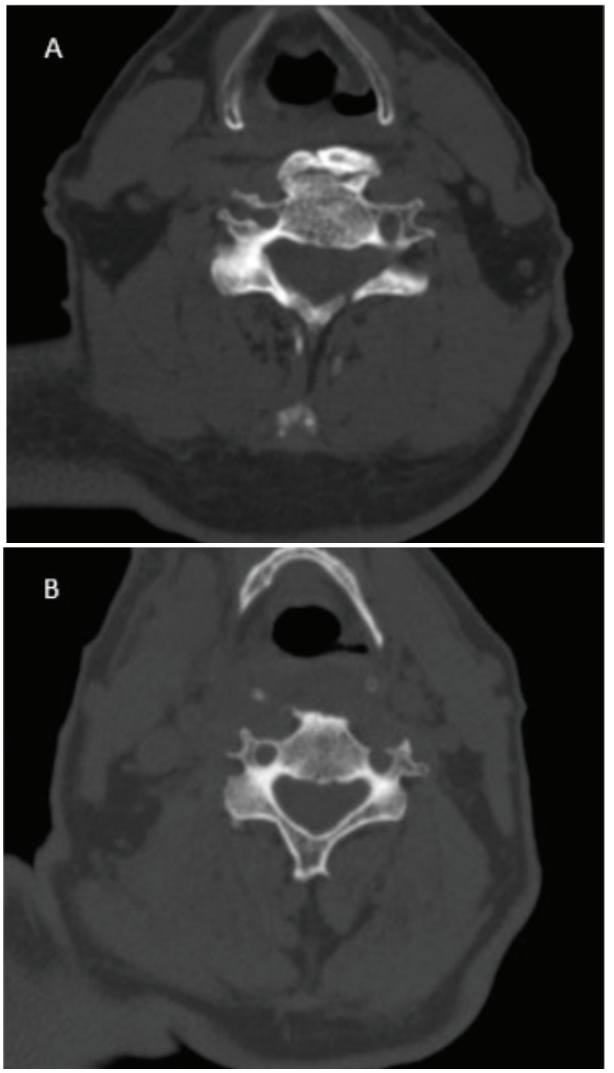

Figure 2: Preoperative (A) and postoperative (B) axial CT scans show total removal of anterior cervical osteophyte

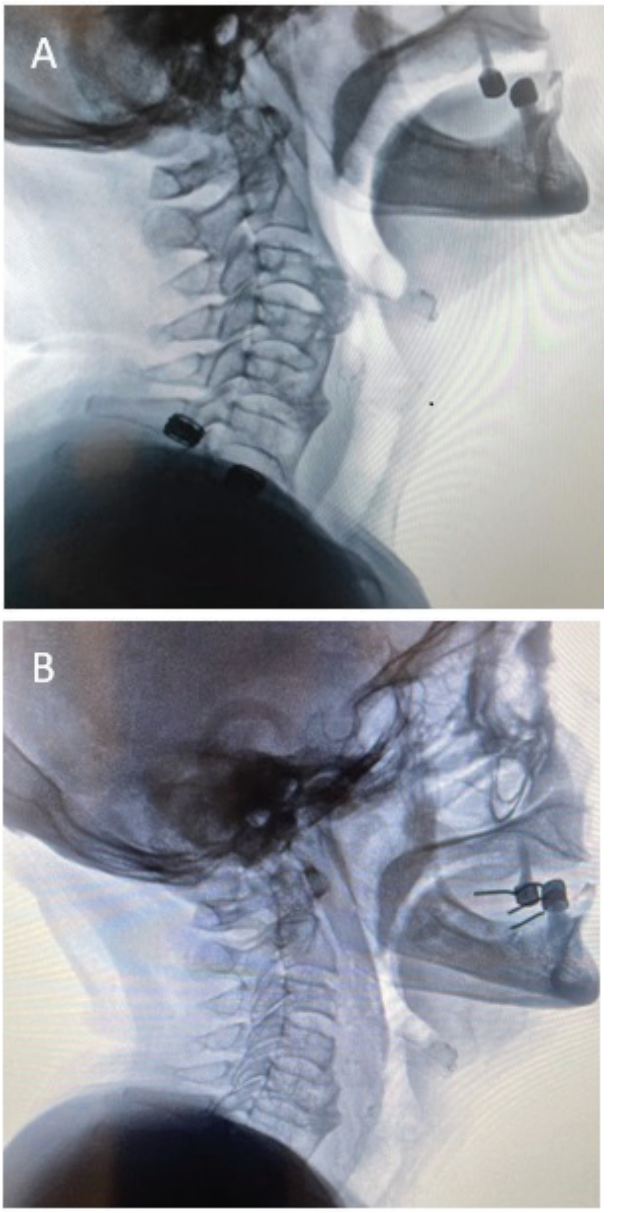

Figure 3: Lateral cervical X-ray of a patient with diffuse idiopathic skeletal hyperostosis (A). Same patient after undergoing anterolateral cervical osteophyte resection (B)

The radiological diagnostic criteria suggested by Resnick and Niwayama for diffuse idiopathic skeletal hyperostosis: the presence of following ossification of the anterior longitudinal ligament of at least four contiguous vertebral bodies, the preservation of intervertebral disc height, and the absence of other signs of degenerative spine joint diseases (8). The differential diagnosis of dysphagia includes tumors of the larynx, pharynx, mediastinum, spine, lung or esophagus, esophageal motility disorders, esophageal strictures, aberrant vessels, and esophageal diverticula. These pathologies can be masked by DISH and should be considered a possible coexistent pathology (14).

It is primarily seen in the C4-7 level in the cervical region (9). In the reviewed, the involved regions were C3-4, C2-3, C6-7, C3-7, and C3-D3. The most frequent symptoms seen in Forestier's disease are neck rigidity, pain, hoarseness, stridor, and dysphagia (15–17). Dysphagia is encountered in 0.6-1% of patients diagnosed with Forestier's disease. Dysphagia appears especially in lower cervical levels, mainly at C4-5 (7,18,19). Case 2 is a rare situation representing an upper cervical area, C2-3. The dysphagia results from pharyngeal and esophageal compression and inflammation in paravertebral and paraesophageal tissues. In addition, stridor, dyspnea, and aspiration may be seen in Forestier's disease (20). Extraspinal involvement, such as the pelvis, calcaneus, olecranon, and patella (20).

Computed tomography (CT) is the gold standard in diagnosis (8). The relationship between osteophytes and adjacent anatomical structures may be shown clearly. In the reviewed cases, a CT scan was used to show that compression on the esophagus causes dysphagia. We also used esophagoscopy, X-rays, and an MRI for evaluation. Some clinicians suggest using endoscopy, but this might be dangerous and has been a cause of esophageal perforation since esophageal wall can be thinned in involved locations (21,22). In our experience, these imaging modalities are sufficient to evaluate the bony structures and soft tissue compression, especially in the esophagus and trachea. The anterior osteophytosis usually involves multiple vertebral levels, but the compression and the related symptoms might not be in all levels.

In DISH cases, conservative treatments are recommended if the patient does not have symptoms and neurological deficits. Nonsteroid anti-inflammatory drugs, steroids, and myorelaxants are conservative treatment options. Surgical treatment can be an option in cases with progressive dysphagia and dyspnea (23–25). In the reviewed cases, an anterolateral cervical approach was used, providing adequate space for removing the osteophytes. There were no findings of instability, such as spondylolisthesis or fractures. In cases of suspected instability, this approach also allows for applying anterior fusion. Other case series also showed the effectiveness of this approach regarding dysphagia in Forestier's disease. A case series study with nine patients showed the resolution of symptoms in all patients after the anterolateral cervical approach (26). In our experience, osteophytectomy at the symptomatic level is sufficient for patient satisfaction and produces less exposure and inflammation in the postoperative period. A case series of nine patients suggested osteophtectomy in the symptomatic segment, consistent with this study (20). Different approaches for osteophyte resection in Forestier's disease are described, such as the per-oral-transpharyngeal approach (27).

Complications like fistula formation, recurrent laryngeal nerve injury, and instability can occur. Infections in this region by oropharyngeal flora could be a devastating complication, especially if osteomyelitis occurs (28,29). In the presented cases, there were no significant complications. The anterolateral cervical approach is a feasible technique for osteophyte removal and provides symptom relief caused by compression.

CONCLUSION

Forestier's disease presenting with dysphagia is very rare. Surgery may be considered when the symptoms are severe and progressive. Osteophyte resection via an anterolateral cervical approach is a safe and effective option for Forestier's disease.

Ethics Committee Approval: This study was approved by Istanbul Faculty of Medicine Clinical Research Ethics Committee (Date: 03.02.2023, No: 03).

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Conflict of Interest: The authors have no conflict of interest to declare.

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SILENT PATHOLOGY ENDOSALPINGIOSIS: CASE SERIES

SESSİZ PATOLOJİ ENDOSALPİNGİOSİS: VAKA SERİSİ

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ABSTRACT

Objective: The aim of this study was to evaluate the clinical data on endosalpingiosis, which is only pathologically recognized, and which may accompany malignancies and endometriosis.

Material and Method: We collected the data of patients who were pathologically diagnosed with endosalpingiosis between May 2017 and January 2023 in a tertiary health institution. The patient's age, gravida, clinical complaints, imaging findings, presence of known risk factors for endosalpingiosis, the operation performed, and the location of the endosalpingiosis focus were recorded. The postoperative statuses of the patients were provided by hospital records and telephone interviews with the patients.

Result: The data of six female patients between 34 and 62 years of age were analyzed. Two of the patients were in menopause, five had a history of previous abdominal surgery, one had endometriosis, and one patient had endosalpingiosis accompanying high-grade serose ovarian carcinoma.

Conclusion: Considering the increase in synchronous malignancies, we believe that endosalpingiosis should be reported by pathology, especially in cases of endometriosis and those with a history of previous surgery, and the clinician should inform the patient of the presence of this diagnosis.

Keywords: Endosalpingiosis, endometriosis, mullerianosis, ovarian cancer

ÖZET

Amaç: Bu çalışmanın amacı sadece patolojik olarak tanınan ve malignitelere ve endometriosise eşlik edebilen endosalpingiosis ile ilgili klinik verileri değerlendirmektir.

Gereç ve Yöntem: Tersiyer sağlık kuruluşunda Mayıs 2017-Ocak 2023 arası patolojik olarak endosalpingiosis tanısı konmuş hastaların verilerini topladık. Hastaların yaş, gravida, klinik şikayet, görüntüleme yöntemi bulguları, endosalpingiosis için bilinen risk faktörlerinin varlığı, yapılan operasyon, endosalpingiosis odağının yeri kaydedildi. Hastaların operasyon sonrası durumları hastane kayıtları ve hastalar ile yapılan telefon görüşmeleri ile sağlandı.

Bulgular: Altı kadın hastaya ait veriler incelendi. Hastalar 34-62 yaş arasındaydı. İki hasta menapozdaydı. Beş hastada geçirilmiş batın ameliyatı öyküsü vardı. Bir hastada endometriosis de vardı. İki hastada geçirilmiş appendektomi, iki hastada sca öyküsü, iki hastada RİA vardı, bir hastada ektopik gebelik nedeniyle salpenjektomi yapılmıştı. Bir hasta high grade seröz over kanseri eşlik eden endosalpingiosis vardı.

Sonuç: Senkron malignitelerdeki artış göz önüne alınarak özellikle endometriosis vakalarında ve geçirilmiş cerrahi öyküsü olanlarda endosalpingiosisin patoloji tarafından rapor edilmesi gerektiğine ve klinisyenin bu tanı varlığında hastayı bilgilendirmesi gerektiğine inanıyoruz.

Anahtar Kelimeler: Endosalpingiosis, endometriosis, mullerianosis, over kanseri

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INTRODUCTION

Endosalpingiosis, first described by Sampson in 1930, is the presence of columnar ciliary glandular epithelia similar to the tubal epithelium outside the tuba. It is a benign and rare entity that is most commonly seen in the pelvic peritoneum covering the uterus, ovary, and tubule, and less commonly in the omentum, lymph nodes, cervix, etc. (5). It can be seen in many different guises, such as small, round, transparent vesicles, light-colored or red smooth-surfaced peritoneal polyps, or opaque, fimbria-like buds (1). In addition, it can be seen as a single cyst with a flat surface, as sarcoma-like red lesions, or as intrauterine cysts (2).

The frequency of endosalpingiosis is not clearly known due to it not being reported by pathology and the lack of a known method of diagnosis, but in one study, the frequency was found to be 7-12% in gynecological surgeries performed for any reason (3).

The coexistence of endosalpingiosis, endocervicosis and endometriosis is defined as mullerianosis (2). Endosalpingiosis is most commonly seen with endometriosis (40%). It can also be seen with some low-grade and borderline malignancies. In cases not associated with endometriosis, endosalpingiosis and synchronous ovary cancer are seen at a younger age (mean 39 years) (4).

The pathogenesis of endosalpingiosis is not clear. However, multifocal metaplasia from the mesothelium, and detection in the lymph node in male patients with prostatic carcinoma supports mullerian metaplasia. Another theory is tubal mucosal implantation. The fact that endosalpingiosis is more common in patients with a previous surgical history supports this theory. Three quarters of those with endosalpingiosis have a history of surgery (6).

Complaints associated with endosalpingiosis may be related to the accompanying disease. In addition, symptoms related to the affected organ such as menorrhagia, abnormal uterine bleeding, abdominal distension, difficulty urinating, and polyuria may be observed. In a gynecological evaluation, this condition can be confused with leiomyoma, adenomyoma, adenocarcinoma, uterine sarcoma, peritoneal tumors, and ovarian cancer (2).

Since biomarkers similar to those for a tubal tumor are secreted in endosalpingiosis, it has been named in the literature as a low-grade or borderline tubal tumor. Studies have shown that ovarian and uterine cancers increase, especially clear-cell carcinomas and mucinous tumors, depending on the capacities of cells with metaplasia in endosalpingiosis cases (3). Nevertheless, endosalpingiosis is a non-neoplastic pathology, and radical oncological surgery is not recommended for the treatment of it.

Our aim in this study is to draw attention to the fact that endosalpingiosis is a pathology that can develop in the genital and other organs and tissues and may accompany malignancy and endometriosis.

MATERIAL and METHODS

This retrospective study was started after the approval of the ethics committee (Date: 13.04.2023, No: 387), and verbal and written consent was obtained from the patients included in the study. The data of six patients who were operated on due to gynecological complaints at the Gynecology and Obstetrics Clinic of the tertiary center between May 2017 and January 2023 and were diagnosed with endosalpingiosis in the pathological examination were collected and evaluated through hospital records and interviews with the patients themselves.

The age, gravida, menopausal status, previous surgery history, previous malignancy history, admission complaint, remarkable laboratory value, ultrasonography and magnetic resonance imaging and Doppler findings (if performed), surgery performed, pathological diagnosis accompanying gynecological pathology, and postoperative conditions of the patients were recorded.

RESULTS

The data of six female patients diagnosed with endosalpingiosis over five years were analyzed. These patients were aged between 34 and 62 years, two of whom were in menopause.

Endosalpingiosis was found in the resected sigmoid colon serosa in one patient, in the ovary in two patients, in the paraovarian area in one patient, in the pelvic lymph node in another patient, and in one patient, endosalpingiosis was in the perimetrium.

All the patients had had a previous pregnancy.

Five patients had a history of previous abdominal surgery. Two patients had previous appendectomy, two had a history of sectio caesarea abdominalis (SCA), two had intrauterine devices (IUDs), and one had a salpingectomy due to an ectopic pregnancy. One patient had endosalpingiosis accompanying high-grade serose ovarian cancer.

One patient also had synchronous endometriosis. There were paratubal cysts in three patients.

There was no additional medicine used by the patients.

Two of the patients had abnormal uterine bleeding and one had postmenopausal bleeding.

Preoperative peritoneal nodularity was suspected in one of the patients, and in the other patients it was found incidentally.

Total abdominal hysterectomy and bilateral salpingo-oopherectomy were performed on five patients. One patient was diagnosed during sigmoid colon surgery.

Information about the patients, their previous surgery history, and pathological features are shown in Table 1.

Except for the appearance of peritoneal nodules in one patient, there was no feature that aroused suspicion of endosalpingiosis in the USG, Doppler and MRI images of the patients.

All of the patients are alive, including the ovarian cancer case.

DISCUSSION

The median age at diagnosis of endosalpingiosis is 50-52 years (10). The patients in the study were on average 47 years old.

There is more than one theory for the etiology. While the metaplasia theory is valid in some patients as it can accompany malignancy and borderline tumors, the explanation in women who have undergone tubal surgery, women with abnormal uterine bleeding and women using IUDs is the tubal cell implantation theory.

Endosalpingiosis has no known macroscopic or imaging features, and often millimetric structures are seen as vesicular effects (1). Diagnosis is made only by microscopic examination. In the study, there was no remarkable abnormality except for paratubal cysts in three patients and a purpura-like lesion on the tubal surface in one patient. Although ultrasonography was performed on all patients and MRI imaging was performed on some patients, endosalpingiosis was diagnosed microscopically in only one patient with suspected peritoneal nodularity on MRI.

Although endosalpingiosis is a benign and silent pathology, it is important in terms of the possibility of accompanying pelvic serous neoplasms (such as lesions of low malignant potential, or low-grade pelvic serous carcinoma). Some data suggest that endosalpingiosis is more common in women with BRCA mutations. In a study that found endosalpingiosis in 86% of BRCA carriers who underwent risk-reducing salpingo-oophorectomy, endosalpingiosis was reported in 56% of women at low risk of ovarian cancer who underwent salpingo-oophorectomy for other indications (7). Our 39 years old patient had high-grade serose ovarian carcinoma (HGSCa) as well as endometriosis and endosalpingiosis. It is seen in the literature that there is a relationship between borderline ovarian tumor (BOT) and endosalpingiosis. However, endosalpingiosis was not detected in our BOT patients in that study (8). In the literature, an increase in malignancies accompanying endosalpingiosis in premenopausal women is mentioned. In our study, we found endosalpingiosis as well as endometriosis and HGSCa in one young premenopausal patient, which may make it meaningful to perform frozen lesion next to a pathology that is thought to be of no clinical importance.

We believe that performing a biopsy for abnormal appearances, such as atypical cystic, nodular polypoid appearances, or increased vascularity in a patient who has been operated on for any reason, may help determine the malignancy risk at that time or later. The prevalence of serous borderline, invasive mucinous, and clear cell histological subtypes is increased in patients with ovarian cancer and endosalpingiosis.

Table 1: Demographic clinical characteristics of the patients

Number	Age (years)	Gravida (n)	Operation-indication	Post-surgery time	Risk factors	Place
1	34	4	Sigmoid colon resection-diverticule perforation	4 years	Appendectomy-intrauterine device	On the colon serosa
2	49	4	TAH+BSO-myoma uteri and abnormal uterine bleeding	6 years	Umbilical hernia operation-endometrial probe curettage	On the ovary
3	53	1	TAH+BSO-myoma and postmenopausal bleeding	5 years	Ectopic pregnancy (salpingectomy)	Bilateral ovaries
4	39	1	Debulking-ovarian Ca and abnormal uterine bleeding	2 years	Appendectomy-Intrauterine device	On the pelvic lymph node
5	62	6	TAH+BSO-postmenopausal bleeding and endometrial hyperplasia	5 years	None	On the ovary
6	45	3	TAH+BSO-myoma	6 years	Bilateral tubal ligation-SCA	Perimetrium

TAH: total abdominal hysterectomy BSO: Bilateral salpingo-oophorectomy, y: SCA: Sectio caesarea abdominalis

Transplantation of the tubal mucosa to the peritoneum in patients with a history of previous surgery or excessive proliferation and healing after tubal surgery is thought to be effective (6). Five of the six patients included in this study had a history of abdominal surgery.

We encountered endosalpingiosis, defined as mullerianosis, with additional endometriosis in one of our patients. Mullerianosis supports an embryological etiology (9). Endometriosis occurs simultaneously in more than one-third of patients with endosalpingiosis.

Although there is information about the regression of endosalpingiosis when the ovaries are removed, two of the patients in this study were in menopause. This supports a hormone-independent etiology (6).

The small number of cases in this clinical study prevents us from defining the clinical presentation of complaints of endosalpingiosis and classifying the accompanying pathologies. However, endosalpingiosis, which is considered to be clinically insignificant, cannot easily be diagnosed due to unperformed biopsies and is recognized only by examining a large area in organ removal surgeries. Our study is, therefore, retrospective and still valuable.

In many cases operated for gynecological reasons, it is not easy to decide whether to perform cystectomy, oophorectomy or salpingo-oophorectomy. Especially if some patients have peritoneal or tissue lesions suggestive of endosalpingiosis, it may be easier to decide by considering the endosalpingiosis malignancy relationship (for example, salpingectomy instead of tubal ligation, or oophorectomy instead of cystectomy).

In this study, we wanted to draw attention to the importance of accurate reporting of endosalpingiosis by pathologists, especially in cases of endometriosis and those with a previous surgical history, considering the increase in synchronous malignancies.

Ethics Committee Approval: This study was approved by Medipol University Non-Interventional Clinical Researches Ethics Committee (Date: 13.04.2023, No: 387).

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EARLY HISTOPATHOLOGICAL COMPARISON OF SINGLE VERSUS DOUBLE-LAYER CLOSURE OF UTERINE INCISION DURING CESAREAN: A CONTROLLED STUDY IN RATS

SEZARYEN SIRASINDA UTERUSUN TEK YA DA ÇİFT KAT KAPATILMASININ ERKEN HİSTOPATOLOJİK KARŞILAŞTIRILMASI: RATLARDA KONTROLLÜ ÇALIŞMA

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ABSTRACT

Objective: Long-term complications of cesarean delivery are numerous and are increasing due to the high cesarean rate. The long-term complications are attributed to the different suturing methods. The single-layer locked (SLL) and double-layer unlocked (DLU) are the most compared. This study aims to compare the early histopathological properties of these two suture techniques in an experimental animal study.

Material and Method: Ten pregnant Wistar-Albino rats had cesarean at term. The right uterine horns were repaired using the SLL suture technique, and the left ones were repaired using the DLU technique. The control subjects were the six uterine horns of three pregnant rats delivered vaginally. Each animal underwent a hysterectomy on day 15 of pregnancy, and each uterus was an experimental unit. The mean thickness of the endometrium and myometrium of the intervention groups with histopathological features and controls were compared.

Result: In SLL and DLU groups, the endometrium (276.6±123.1 vs. 258.4±125.9 μm; p=0.748) and myometrium (531.7±189.2 vs. 505.9±182.1 μm; p=0.612) in scarred areas were similar. In non-scarred areas, the endometrium was measured as 239.9±68.9, 256.5±127.2, and 316.4±98.6 μm in SLL, DLU, and control group, respectively (p=0.347). The myometrium of non-scarred areas

ÖZET

Amaç: Sezaryenin birçok uzun dönem komplikasyonu vardır. Yüksek sezaryen oranları nedeniyle bunlar artmaktadır. Uzun dönem komplikasyonların farklı sütür teknikleri ile ilişkisi olduğu düşünülmektedir. Tek kat kilitlenerek (SLL) ve çift kat kilitlenmeden (DLU) en çok karşılaştırılan yöntemlerdir. Bu çalışmanın amacı iki farklı sütür tekniğinin erken dönem histopatolojik sonuçlarını bir deneysel hayvan modelinde karşılaştırmaktır.

Gereç ve Yöntem: On Wistar-Albino rata miadında sezaryen yapıldı. Sağ uterus SLL, sol uterus DLU olarak kapatıldı. Kontrol grubunda ise normal doğum yapmış üç ratın altı uterusu bulunmaktaydı. Doğumdan 15 gün sonra tüm hayvanlara histerektomi yapıldı ve her bir uterus deney ünitesi olarak kullanıldı. Çalışma ve kontrol grupları arasında endometrium ve myometrium ortalama kalınlıkları ile histopatolojik özellikler karşılaştırıldı.

Bulgular: SLL ve DLU gruplarında endometrium (276,6±123,1 vs 258,4±125,9 μm; p=0,748) ve myometrium (531,7±189,2 vs 505,9±182,1 μm; p=0,612) skarlı alanda benzer kalınlığa sahipti. Skarsız alanda SLL, DLU ve kontrol gruplarında endometrium kalınlığı sırasıyla 239,9±68,9; 256,5±127,2, ve 316,4±98,6 μm olarak ölçüldü ve benzer olarak değerlendirildi (p=0,347). Benzer şekilde skar olmayan alanda SLL, DLU ve kontrol gruplarında myometrium kalınlığı da benzerdi (387,2±119,9;

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was also similar in all groups evaluated (387.2±119.9; 364.5±154.1 and 234.0±49.1 μm; p=0.265). The histopathological features of uteri repaired with two different techniques were also similar.

Conclusion: The early histopathological properties of all uteri examined were similar after repairing with SLL or DLU techniques. These results indicate that the repair process does not differ in the early stages, regardless of the uterine closure technique used.

Keywords: Surgical technique, uterine closure, cesarean section, pregnancy, histopathology

364,5±154,1 ve 234,0±49,1 μm; p=0,265). İki farklı teknikle kapatılan uterus örneklerinin histopatolojik özellikleri de benzerdi.

Sonuç: SLL ve DLU teknikleri ile uterus kapatıldıktan sonra uterusların erken dönem histopatolojik özellikleri benzer olarak değerlendirildi. Bu sonuçlara göre uterus nasıl kapatılırsa kapatılsın erken dönemde iyileşme sürecinin etkilenmediğine işaret etmektedir.

Anahtar Kelimeler: Cerrahi teknik, uterusun kapatılması, sezaryen, gebelik, histopatoloji

INTRODUCTION

In 1916, Professor Edwin Bradford CRAGIN first proposed the idea of "once cesarean, always cesarean." With the introduction of fetal monitoring in the delivery wards, the cesarean section (C/S) rate increased incrementally from the mid-1970s. Today, nearly 1.2 million babies are born annually in Turkiye, and more than half are delivered by C/S, corresponding to 74 operations every hour (1). However, while Turkiye is one of the world leaders in C/S rates, only a few countries have reached the World Health Organization's goal of 10-15% since 1985.

By the mid-1990s, the trial of labor after cesarean (TOLAC) trend gained popularity, and total C/S rates decreased. However, this trend could survive only one decade due to fear of the catastrophic outcomes of uterine rupture, which is not more than 1%. Therefore, nowadays, healthcare providers and patients stand aloof from TOLAC (2). From a historical perspective, the uterine incision has shifted from the vertical to the low transverse; suture material has moved from the chromic catgut to polyglactin 910, and the closure technique has changed from the double-layer to single-layer. The change in choice for suture material and closure technique almost coincided with the popularity of TOLAC. Consequently, the investigators questioned the possible relation between the uterine rupture during TOLAC and the uterine closure technique. In the last two decades, many attempts have been made to find the proper way for uterine closure in C/S (3-18). In this experimental animal study, we aimed to investigate the early histopathological properties of the uterus in rats exposed to the two most preferred uterine closure techniques (single-layer locked *versus* double-layer unlocked) in C/S.

MATERIAL and METHODS

Virgine, female Wistar albino rats, aged three months and weighted 200-250 g, were included in the study. Each animal was housed in a separate cage in a heat-stabilized room at 22-24°C from the first day of pregnancy diagnosis. A standard laboratory diet and water were allowed *ad libitum*. The weight of each rat was measured daily, and its general condition was monitored. The rats were divided into study and control groups according to their order in the experiment. After C/S was administered to the first three rats, the rest were allowed to give birth spontaneously. In other words, rats numbered 1, 2, 3, 5, 6, 7, 9, 10, 11, and 13 were allocated to the study groups, and 4, 8, and 12 were allocated to the control group.

The average gestation period in rats is 22-23 days and C/S was not performed before day 20 of pregnancy. The rats were anesthetized by the injection of 40 mg/kg ketamine hydrochloride (Ketalar® 500 mg, Pfizer PFE İlaçları, İstanbul, Turkiye) and 5 mg/kg xylazine hydrochloride (Xylazin Bio® % 2, Bioveta, Czechia) into the peritoneum. A midline vertical incision was performed to access the abdomen. Each uterine horn was examined before the incision. An incision 1.5-2 cm in length was made on the anti-mesenteric side of the uterus. All embryos were removed with their adjacent tissues and maternal hemostasis was secured. The number of fetuses in each uterine horn was recorded. The uterine incisions were closed with multifilament 4/0 polyglactin 910 (Pegalak®, Doğsan, Trabzon, Turkiye) on both uteri. An indicator, a non-absorbable suture, was placed 0.5 cm above the upper border of the uterine incision with 4/0 polypropylene (Propilen®, Doğsan, Trabzon, Turkiye). On the right side single-layer, continuous, locked suture technique was applied to close the uterus, and on the left side double-layer, the continuous, unlocked technique was employed. For prophylaxis of surgical site infection, 60 mg of ampicillin (Ampisid® 250 mg, Mustafa Nevzat İlaç Sanayii, Istanbul, Turkiye) was injected into the peritoneum and then the abdominal incision was closed using 3/0 polyglactin 910 (Pegalak®, Doğsan, Trabzon, Turkiye). The skin incision was closed using a separate stitch of 4/0 polypropylene. The animal was kept under a heater until it fully recovered from anesthesia. Rats were determined to be hemodynamically stable and housed in their cage. The antibiotic prophylaxis continued for two more days with an intraperitoneal injection of 30 mg of ampicillin. Exclusion criteria were that the rat died before the day of the hysterectomy, or the specimen was of poor quality. The delivered mice naturally formed the controls.

All animals underwent hysterectomy on the postpartum 15th day. First, the anesthesia was administered as stated previously, then the abdominal cavity was opened. Each uterus specimen was preserved and labeled in a 10% formaldehyde solution. Samples were embedded in paraffin blocks and 5 µm sections were cut using a rotary microtome, after which an automated system stained them with hematoxylin-eosin and Masson's trichrome stain (Leica ST 5020, Leica Biosystems Nussloch, Germany). The histopathological examinations were performed by one expert. The quantitative outcome parameters on hematoxylin & eosin staining are the thickness of the endometrial lining, muscle layer, and whole uterus on the uterine incision (scarred area) and the opposite of the incision (non-scared area) in C/S samples or controls. Uterine thickness was determined by adding up the endometrial and myometrial thicknesses. The qualitative outcomes with hematoxylin & eosin staining were wound healing, inflammation, collagen deposition, gland density, hemosiderin-laden macrophages, and residual suture material. Collagen formation was stained with Masson's trichrome. The images were transferred to Aperio ImageScope [v12.3.3.5048], and measurements were obtained using a computer-assisted image analyzer. First, three measurements were obtained for each quantitative criterion, and the mean value was calculated. Then, the statistical analysis was performed using the mean values.

The sample size was calculated according to the resource equation in conditions where the standard deviation information was scant, or the effect size specification was problematic (19). The normality of data was checked with the Kolmogorov-Smirnov test. The homogeneity of variances was confirmed by using the Levene test. The normality assumption met one-way ANOVA, or student's t-test was used for comparing groups. For all statistical tests, $p<0.05$ was accepted as significant. Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) 17.0 for Windows.

This study was performed in compliance with the Declaration of Helsinki. The experiments complied with the Turkish Inspectorate of Animal Experiments' guidelines for using and caring for laboratory animals and were approved by the Local Ethics Committee of Laboratory Animal Use and Committee of the University of Cukurova (Date: 10.12.2020, No: 9). The ARRIVE guidelines for animal research are followed (20).

RESULTS

Thirteen pairs of the uterus have been obtained. Of these uteri, 10 single-locked, 10 double-locked, and six control were prepared for pathological examination. The descriptive properties of animals are depicted in Table 1.

Compared to controls, two weeks after C/S, the endometrial layer of the repaired uterus become thinner. However, the thickness of the endometrium was similar regardless of the suture technique used. While the endometrial layer got thinner compared to controls after C/S, the myometrium and uterus got thicker. However, these differences still did not reach a significant level. Furthermore, the thickness of the myometrium and the total thickness of the uterus were similar. The measurements obtained at the microscope are presented in detail in Table 2. Figure 1 depicts one sample from each group.

The macroscopic appearance of uteruses in both suturing techniques was similar. Wound integrity was formed in almost all uteruses in two weeks except for one uterus in the single-layer locked group. Collagen deposition was observed in the majority of specimens in both groups. Endometrial gland density also appeared to be normal in both groups. While there was more lymphocytic infiltration in the single-layer locked group, it did not reach a statistically significant level. In eight samples from each group, hemosiderin-laden macrophages were present. Remnant sutures were present in nearly all specimens at the end of two weeks. Tissue healing and collagen deposition were complete before the suture materials were entirely lost. The histopathological features of the scarred uteruses are displayed in Table 3.

Table 1: Descriptive data of experimental animals in all groups

	Cesarean (n=10)	Normal (n=3)
	Mean±SD (Median)	Mean±SD (Median)
Gestational age at delivery (days)	21.8±0.9 (21)	24.3±0.6 (24)
Weight on the first day of pregnancy (g)	231.5±29.7 (234)	223.0±12.8 (223)
Weight on the day of delivery (g)	278.9±25.6 (275)	267.3±18.9 (263)
Weight on the day of hysterectomy (g)	215.3±18.5 (214)	250.0±29.1 (257)
Litter (#)	9.1±0.9 (9)	9.0±1 (9)

SD: Standard deviation, #: Number

Table 2: Comparison of the thickness of endometrium, myometrium and uterus among the groups

	Endometrium		Myometrium		Uterus	
	Non-scarred (µm)	Scarred (µm)	Non-scarred (µm)	Scarred (µm)	Non-scarred (µm)	Scarred (µm)
Single-layer locked (n=10)						
Mean±SD (Median)	239.9±68.9 (238.8)	276.6±123.1 (280.3)	387.2±119.9 (392.1)	531.7±189.2 (536.4)	627.2±159.5 (669.2)	802.3±135.1 (799.4)
Double-layer unlocked (n=10)						
Mean±SD (Median)	256.5±127.2 (250.5)	258.4±125.9 (292.4)	364.5±154.1 (385.7)	505.9±182.1 (509.5)	620.9±234.4 (631.4)	786.4±248.4 (770.2)
Control (n=6)						
Mean±SD (Median)	316.4±98.6 (306.9)	-	234.0±49.1 (225.9)	-	550.4±144.2 (532.9)	-
p[a]	0.347	0.748	0.265	0.612	0.408	0.767

SD: Standard deviation, [a]: One way ANOVA or student's t test was performed

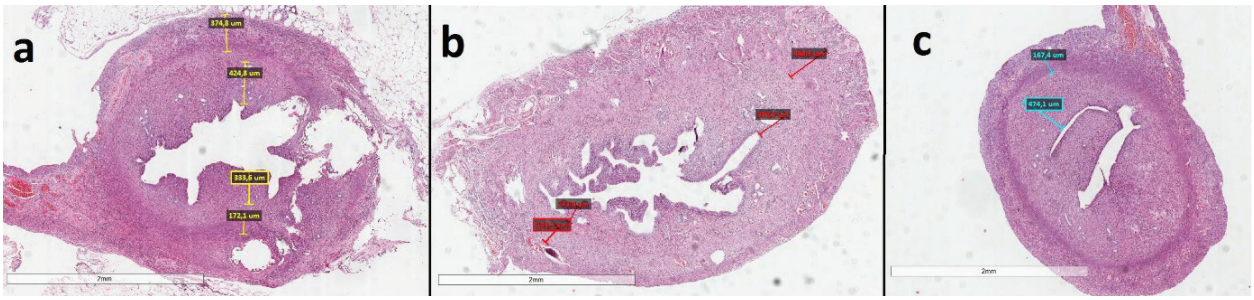

Figure 1: From left to right, images a, b, and c depict a sample from single-layer locked, double-layer unlocked, and control groups, respectively.

DISCUSSION

The basics of wound healing consist of five phases: hemostasis (first few minutes), inflammation (ends within three days), epithelization or migration (ends within two days), fibroplasia (the fibroblasts produce collagen; it reaches its maximum at the fifth day and continues for at least six weeks) and maturation (the main action is the collagen remodeling which takes approximately six months). The synthesis of collagen fibers depends on the events occurring in the injury's first week. The interaction between the collagen fibers determines wound strength. However, uterine wound healing in C/S shows some uniquity. The high input of blood supply decreases significantly and rapidly; the size of the human uterus diminishes and becomes non-palpable in the true pelvis by the 9th day of puerperium, and the endocrine environment shifts to the non-pregnant status. In humans, the involution, as a summary of these steps, is generally completed within two to three weeks. The uterine involution is faster than the wound healing. The rapid shrinkage of the uterus makes the sutures hang in the space within a few weeks.

Most recent publications use radiologically measured thickness as a determinator of tissue healing. However, the radiological examination did not definitively determine tissue structure, niche-related symptoms, and uterine rupture resistance in the subsequent pregnancy. Rozenberg et al. have stated that transabdominal ultrasonography measurement of the thickness of the lower uterine segment before the delivery does not lower maternal and perinatal adverse results (21). The methodology of measurement is another issue, Bolten et al. have demonstrated that the combined use of transvaginal ultrasound and magnetic resonance imaging is a reproducible tool for examination of the lower uterine segment following C/S, but the transabdominal approach is not (22). Therefore, the data needs to be more consistent. Some observations depicted a thicker lower uterine segment, and less niche occurs with a double layer; others did not (5,12,13,16). Our results showed that the suturing techniques did not differ between tissue thickness and histopathological features. The wound integrity and adequate collagen deposition were obtained in both groups. On the other hand, the residual sutures are still present in the majority.

Table 3: The histopathological features of the uteruses in the study groups

	Single-layer locked (n=10)	Double-layer unlocked (n=10)	p
Macroscopic appearance			
Normal	8	8	0.999
Inflamed, necrotic	2	2	
Wound integrity			
Present	9	10	0.305
Absent	1	0	
Collagen			
Present	8	7	0.606
Absent	2	3	
Gland density			
Normal	8	6	0.329
Absent	2	4	
Inflammatory lymphocytes			
Present	9	6	0.121
Absent	1	4	
Hemosiderin-laden macrophages			
Present	8	8	0.999
Absent	2	2	
Residual suture			
Present	9	7	0.264
Absent	1	3	

SD: Standard deviation

The uterine wound healing after C/S has been evaluated using different parameters. These are measuring residual myometrial thickness and/or demonstration of uterine niche in symptomatic or asymptomatic patients radiologically (transabdominal and/or transvaginal ultrasound, magnetic resonance imaging, hysterogram, sonohysterography); direct observation during the next C/S (tissue thickness, uterine rupture, or dehiscence); uterine rupture during TOLAC and development of abnormal placental invasion. To our knowledge, any study investigating the risk of scar pregnancies regarding the suture technique has not been published yet. Bujold et al. have retrospectively evaluated the risk of uterine rupture during the TOLAC and found that the risk was nearly fourfold after single-layer (23). A meta-analysis of 12 trials has been published by Roberge et al. The authors have stated that the risk of uterine rupture at TOLAC was similar between single-layer versus double-layer and single-layer unlocked versus double-layer. However, the risk of uterine rupture is five times higher in a single-layer locked than in a double-layer (7). On the other hand, Hesselman et al. compared 2589 patients with single-layer to 5002 patients with double-layer. This large's study outcomes signify no difference in uterine rupture at TOLAC regarding the suture technique (14). Sumigama et al. have stated that the risk of placenta accreta is six times higher when the uterus is closed continuously instead of interrupted sutures (15). This is the only study evaluating suturing techniques' role in the development of placenta accreta.

Studies evaluating the histopathological appearance of uterine wounds are focused on the long-term consequences of the C/S scar (24-26). However, none of them made a comparison regarding the layer count of the uterine suture. Lapointe-Milot et al. compared the histopathological features of the uterus after single-layer *versus* double-layer uterine closure in a sheep model (27). Due to placental features, the uterus was closed while the placenta was still in place. The early stages of wound healing would not be comparable to humans due to this dissimilarity.

According to our observations in this study, we believe uterine wound healing is not solely related to suturing technique. The number of possible suturing techniques takes into account many parameters. For single-layer, there are six possibilities: continuous, locked ± endometrial layer (2); continuous, unlocked ± endometrial layer (2); interrupted ± endometrial layer (2). Three more options accounted for the outer layer of the double-layer suturing. These options are continuous, locked (1); continuous, unlocked (1); interrupted (1). In sum, six times three, there are 18 possibilities for double-layer suturing. Therefore, designing such a study does not seem rational. Additionally, other factors may contribute more than the suturing technique including the site of uterine incision, time of C/S, medical conditions contributing to wound healing like anemia, maternal obesity, premature rupture of membranes, having multiple C/S, post-partum endometritis, hypoalbuminemia, diabetes, and preeclampsia (28). The effects of different uterine closure techniques on the rates of infertility, abortion, preterm delivery, premature rupture of membranes, and bleeding in the subsequent pregnancy may also be the subjects of future investigations. Another future research area should be the surgical technique for multiple C/S. To date, the majority of published data focus on the primary C/S. However, many women experience repetitive C/S, and numerous uterine surgeries increase the risk of uterine rupture and placenta accreta spectrum.

CONCLUSION

To conclude, single-layer locked and double-layer unlocked sutures have similar histopathological features in the early wound healing period. Therefore, while awaiting the studies seeking long-term histopathological and biomechanical outcomes, both techniques seem safe and available.

Ethics Committee Approval: This study was approved by the Local Ethics Committee of Laboratory Animal Use and Committee of the University of Cukurova (Date: 10.12.2020, No: 9).

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RETROSPECTIVE EVALUATION OF DIAGNOSTIC METHODS AND TREATMENT OPTIONS IN AMIODARONE-INDUCED THYROTOXICOSIS

AMİODARONA BAĞLI TİROTOKSİKOZDA TANI YÖNTEMLERİ VE TEDAVİ SEÇENEKLERİNİN RETROSPEKTİF DEĞERLENDİRİLMESİ

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ABSTRACT

Objective: Amiodarone-induced thyrotoxicosis is an important cause of morbidity and mortality that is difficult for physicians to recognize and manage. We retrospectively analyzed the parameters used for diagnosis, classification, and treatment for amiodarone-induced thyrotoxicosis.

Material and Method: We included patients who had amiodarone-induced thyrotoxicosis (AIT). We recorded the demographics, the presence and characteristics of heart and thyroid diseases, the time and dosage of amiodarone exposure, thyroid function tests and thyroid auto-antibodies, and the diagnostic methods and management of thyroid disease.

Result: We included 25 patients (mean age: 64.1±15.3 years, 56% male) who were classified as type 1 (n:12; 48%), type 2 (n:7; 28%), and mixed-type amiodarone-induced thyrotoxicosis (AIT) (n:6; 24%). In the comparison of type 1 AIT to 2 AIT, free T3 and T4 concentrations were 5.1±1.6 pmol/L vs. 7.6±2.4 pmol/L, and 29.2±8.8 pmol/L vs. 34.9±11pmol/L, respectively. Iodine uptake measurements at the 2nd hour were positively correlated with the 24th-hour measurement (p=0.005). Antithyroid drug (n:20) was given for 24 months, glucocorticoid (n:7) and sodium perchlorate (n:5) were given for 7.4±1.7 and 3.5±2 months, respectively. The first treatment option was methimazole for type 1 AIT and methylprednisolone for type 2 AIT. The duration of remission was shorter in type 2 AIT (p=0.009). Five patients had radioactive iodine treatment, and one underwent thyroidectomy.

ÖZET

Amaç: Amiodarona bağlı tirotoksikoz (ABT) hekimler için tanıması ve yönetimi zor, morbidite ve mortalitesi yüksek bir durumdur. Bu çalışmada ABT tanısı, sınıflandırılması ve tedavi için kullanılan parametrelerin retrospektif olarak incelenmesi amaçlanmıştır.

Gereç ve Yöntem: Amiodarona bağlı tirotoksikoz nedeniyle ayaktan tedavi gören hastalar dahil edildi. Demografik özellikler, kalp ve tiroid hastalıklarının varlığı ve özellikleri, amiodaron maruziyetinin zamanı ve dozu, tiroid fonksiyon testleri ve otoantikorları ve tiroid hastalığının tanı yöntemleri ve yönetimi kaydedildi.

Bulgular: Tip 1 (n:12; %48), tip 2 (n:7; %28) ve mikst tip (n:6; %24) ABT olarak sınıflandırılan 25 hasta (ortalama yaş: 64,1±15,3 yıl, %56'sı erkek) çalışmaya dahil edildi. Tip 1 ABT, tip 2 ABT ile karşılaştırıldığında, serbest T3 ve T4 konsantrasyonları sırasıyla 5,1±1,6 pmol/L'ye karşı 7,6±2,4 pmol/L ve 29,2±8,8 pmol/L'ye karşı 34,9±11 pmol/L idi. İkinci saat radyoaktif iyot tutulumu 24. saat radyoaktif iyot tutulumu ile pozitif korelasyon gösterdi (p=0.005). Tedavide sırasıyla, antitiroid ilaç (n=20) 24 ay, glukokortikoid (n=7) 7,4±1,7 ay ve sodyum perklorat (n=5) 3,5±2 ay kullanıldı. Tip 1 ABT için ilk tedavi seçeneği metimazol ve tip 2 ABT için metilprednizolon idi. Tip 2 ABT 'da remisyon süresi daha kısaydı (p=0,009). Beş hastaya radyoaktif iyot tedavisi, bir hastaya tiroidektomi uygulandı.

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Conclusion: The management of AITs is difficult. It should be kept in mind that these patients may need amiodarone again; therefore, ablative treatments should be planned if needed.

Keywords: Amiodarone induced thyrotoxicosis, methimazole, methylprednisolone, perchlorate

Sonuç: Amiodaron ile indüklenen tirotoksikozların yönetimi zordur. Bu hastaların tekrar amiodarona ihtiyaç duyabileceği akılda tutulmalı, bu nedenle ihtiyaç halinde ablatif tedaviler planlanmalıdır.

Anahtar Kelimeler: Amiodaron tirotoksikozu, metimazol, metilprednizolon, perklorat

INTRODUCTION

Amiodarone is a potent antiarrhythmic drug with a structure similar to thyroxine (1, 2). Amiodarone affects thyroid functions in two ways: effects that occur with the intrinsic properties of the drug and effects that are dependent on its high iodine content. While amiodarone causes destructive thyroiditis with a direct cytotoxic effect on thyroid follicles, high iodine content causes inhibition of 5'-deiodinase activity (3-6). Depending on the degree of iodine exposure, some patients remain euthyroid, while others may develop amiodarone-induced thyrotoxicosis (AIT) or hypothyroidism. The incidence of AIT is 1-23% and it can occur early or years after treatment begins (7, 8). Two types of AIT are described: Type 1 AIT occurs due to increased thyroid hormone synthesis because of the iodine excess, type 2 AIT is caused by the destructive thyroiditis. However, mixed-type AIT may have characteristics of both conditions (9,10). Despite the useful findings, it can be difficult to distinguish between types of AIT. Moreover, identification of these types is critical for the management of treatment. Withdrawal of amiodarone may not be possible for type 1 AIT or cardiologists need to restart it. On the other hand, the effect of amiodarone may persist for months after discontinuation due to its long half-life. Antithyroid agents are used until euthyroidism is achieved. In selected patients, sodium perchlorate can be added (11-13). Radioactive iodine (RAI) or thyroidectomy can be radical solutions for type 1 AIT (14).

Glucocorticoids are the choice of therapy for the treatment of type 2 AIT. After the control of thyrotoxicosis, the dose of glucocorticoids should be gradually tapered and discontinued within 2-3 months (15). In cases with stable cardiac status and requiring rapid euthyroidism, discontinuation of amiodarone and resumption after achieving euthyroidism is an option; however, prophylactic thyroid ablation therapies such as RAI or thyroidectomy should be performed before restarting amiodarone. In cases where cardiac status is unstable and amiodarone treatment is necessary, amiodarone should not be discontinued, and salvage thyroidectomy should be considered, if necessary (16-18).

Combined treatment with methimazole and methylprednisolone is the most effective and rapid treatment for mixed-type AIT. Rapid response to treatment leads to diagnose type 2 AIT, while poor response leads to type 1 AIT. Amiodarone-induced thyrotoxicosis is an important cause of morbidity and mortality. There are difficulties in identifying the types of thyrotoxicosis, and management of patients can be challenging. In this study, we aimed retrospectively to evaluate the diagnostic methods and treatment options used in AITs.

MATERIAL and METHODS

In this cross-sectional study, we included patients over 18 who had AIT and were followed-up in our outpatient clinic between 2016 and 2017 for at least three months and who agreed to participate in the study.

We recorded age, gender, underlying heart disease and thyroid disease (if any), number of patients unable to discontinue amiodarone, duration of amiodarone treatment, daily and cumulative amiodarone dose, serum concentrations of free T3 (FT3), free T4 (FT4), thyroid-stimulating hormone (TSH) values at diagnosis, FT4/FT3 ratio, levels and positivity rates of anti-thyroid peroxidase (anti-TPO), anti-thyroglobulin (anti-Tg), thyrotropin receptor antibody (TRAb), initial urinary iodine excretion.

We documented thyroid volume, presence of nodules (if any), and vascularity with ultrasonography (USG). Thyroid volume was calculated with the Ellipsoid formula [Ellipsoid formula: Л/6 × lobe width (cm) × lobe depth (cm) × lobe length (cm)] and summed (19).

We noted the percentages of the 1st, 2nd, and 24th-hour radioactive iodine uptake (RAIU) in I-131 scintigraphy, treatment options [antithyroid drug/glucocorticoid/sodium perchlorate (NaCLO4)] with the dosage, duration, side effects, the type and the protocols of preparation for ablative treatment models, and the final thyroid function (euthyroidism/hypothyroidism/ hyperthyroidism) status with the treatment.

The research protocol was approved by the Istanbul Faculty of Medicine Clinical Research Ethics Committee (Date: 26.05.2017, No: 10). The study was conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (20).

Statistical analysis

All data were analyzed using SPSS software version 21.0 (SPSS Inc, Chicago, IL, license number: 9E5602E4D-B7A4975). Statistical analyses were conducted in accor-

dance with international statistical reporting standards (21). Variables were expressed as mean±standard deviation or median and minimum-maximum, where appropriate. The Chi-square test or Fisher's exact test was used to compare categorical variables. The Student's t-test and adjusted t-test were used to compare independent groups. Pearson's correlation analysis was used to determine whether there was a relationship between dependent and independent variables. One-way ANOVA test was used for the comparison of continuous variables between groups, while Tukey's honestly significant difference test was used for the post-hoc analysis at follow-up.

RESULTS

Of the patients (n=25), 56% (n=14) were male, and the mean age was 64.1±15.3 years. The indication to start amiodarone was atrial fibrillation (n=14; 56%), ventricular tachycardia (n=3; 12%), other tachyarrhythmias (n=3; 12%), and was unknown in 5 (20%) patients. Twenty-two (88%) patients had no known thyroid disease before starting amiodarone, while 1 (3%) had a history of hyperthyroidism, 1 (3%) multinodular goiter, and 1 (3%) hypothyroidism. The duration of amiodarone treatment was 21 months (range=3-156), the mean daily and cumulative dose were 197±56 mg and 106.450 mg (range=3.000-949.000), respectively.

Patients were classified as type 1 (n=12; 48%), type 2 (n=7; 28%), and mixed-type AIT (n=6; 24%). In the comparison of type 1 to 2 AIT, FT3, FT4, and TSH concentrations were 5.1±1.6 pmol/L vs. 7.6±2.4 pmol/L, 29.2±8.8 pmol/L vs. 34.9±11pmol/L, and 0.09±0.02 vs. 0.04±0.01 mIU/L, respectively.

The initial FT3 concentration was positively correlated with the FT4 concentration (r=0.709, p<0.002) and was negatively correlated with the iodine uptake measurement at the 2nd hour (r=-0.964, p<0.001), whereas no significant correlation was found among the cumulative amiodarone dose, initial TSH concentration, iodine uptake measurement at the 1st and 24th hours, thyroid volume, and methimazole dose used (p>0.05). A negative correlation between FT4 and TSH concentration (r=-0.860, p<0.001) and a positive correlation between FT4 concentration and methimazole dose (r=0.539, p=0.035) were found, while no significant correlation was found among TSH concentration, iodine uptake measurement at the 1st, 2nd, and 24th hours, and thyroid volume (p>0.05).

When the iodine uptake tests were compared, a positive correlation was found between the 2nd and 24th-hour iodine uptake (r=0.774, p=0.005).

The initial 24-hour urinary iodine excretion was 1142.3±340 µg/day in patients with type 1 AIT and 3329.5±1100 µg/day in patients with type 2 AIT; there was a statistically significant difference between the two groups (p=0.002) (Table 1).

Among the thyroid auto-antibodies, anti-TPO and anti-Tg were measured in 22 patients (88%) and TRAb in 11 (44%) patients. On USG (n=19) no nodule (n=9), solitary nodule (n=2), and multiple nodular goitre (n=3) were reported.

It was not possible to discontinue amiodarone treatment in six patients (24%) after the diagnosis of thyroid dysfunction. We found no significant difference for duration and cumulative dose of amiodarone, initial FT3, FT4, TSH levels, time to euthyroidism, and iodine uptakes at the 1st, 2nd, and 24th hours when we compared the patients who continued and discontinued amiodarone.

Antithyroid drugs (n=20) were given for 24 months (range=1-120), while sodium perchlorate (n=5) was administered for three months (range=1-6). Methylprednisolone or equivalent glucocorticoid was initiated in seven patients. The daily dose and the duration was 25.5 mg (range=15-40) and 7.4 months (range=2-12), respectively.

In terms of the side effects during AIT treatment, absolute agranulocytosis and thrombocytopenia developed in one of the 25 patients. One patient had multiple vertebral fractures due to the glucocorticoid-induced osteoporosis, while no side effects were detected in patients using sodium perchlorate.

Euthyroidism in 14 (56%), subclinical hypothyroidism in 5 (20%) patients were achieved after medical treatment. However in six of them (24%) hyperthyroidism could not controlled with medical treatment. The time to euthyroidism was seven months (range=1-36), and the duration of remission was significantly shorter in type 2 AIT compared to type 1 AIT (5.6±1.4 vs. 13.3±3.8 months, p=0.009) (Table 1).

Five patients had RAI treatment, and one patient underwent thyroidectomy as a radical treatment. The mean RAI dose was 30±8 mCi. Repeated doses were needed in two patients because of persistant hyperthyroidism. The comparison of patients with type 1 and 2 AIT data was given in Table 1.

Of the patients who we could not classify as type 1 or 2 AIT and thus were defined as mixed-type AIT, 50% were female, and the mean age was 63±20 years. Only one patient in this group continued amiodarone after the diagnosis of AIT. The median duration of amiodarone treatment was 18 months (range=4-36), and the median daily dose was 200 mg (range=50-400). Free T3, FT4, and TSH levels were 9.6 pmol/L (range=5.3-14.8), 46.5 pmol/L (range=12-100), and 0.01 mIU/L (range=0-23), respectively. The anti-TPO, anti-Tg, and TRab values were 11 IU/mL (range=5.6-21), 186.5 IU/mL (range=10.8-480), and 1.5 IU/L

Table 1: The comparison of patients with type 1 and 2 amiodarone-induced thyrotoxicosis

Variables	Type 1 AIT (n=12)	Type 2 AIT (n=7)	p
Age (years)	64.2±11.6	64.7±18.9	0.773
Gender (F/M)	5/7	3/4	0.090
Number of patients unable to discontinue amiodarone	4	1	0.510
Duration of amiodarone used (months)	36 (4-156)	20.5 (3-108)	0.884
Dose of amiodarone (mg/day)	190.9±30.1	200	0.090
Free T3 at diagnosis (pmol/L)	5.1±1.6	7.6±2.4	0.140
Free T4 at diagnosis (pmol/L)	29.2±8.8	34.9±11	0.211
Free T4/Free T3 ratio	5.2 (3.7-52.7)	4.7 (3-6.6)	0.710
TSH at diagnosis (mIU/L)	0.09±0.02	0.04±0.01	0.482
Anti-TPO (IU/mL)	11±3.3	10.9±3.1	0.958
Anti-Tg (IU/mL)	183.6±59	209±67	0.860
TRAb (IU/L)	0.7 (0.01-4.4)	2.3 (0.01-4.7)	0.980
Anti-TPO positivity (n, %)	10 (40)	6 (24)	0.632
Anti-Tg positivity (n, %)	10 (40)	6 (24)	0.436
TRAb positivity (n)	2	1	0.944
Time to euthyroidism (months)	13.3±3.8	5.6±1.4	**0.009***
Thyroid volume (cm^3)	39 (18-72)	12 (10-30)	0.229
Increased vascularity in Doppler USG (n)	4	2	0.260
Presence of nodules (n)	8	1	0.235
RAIU 1. hour (%)	1.6±0.5	1.5±0.4	0.200
RAIU 2. hour (%)	1.9±0.6	1.4±0.1	**0.020***
RAIU 24. hour (%)	1.7±0.5	1.2±0.3	0.920
Initial 24-hour urinary iodine excretion (µg/day)	1142.3±340	3329.5±1100	**0.002***
Number of patients using methimazole	9	4	0.260
Dose of methimazole (mg/day)	10 (5-15)	22.5 (15-30)	0.513
Number of patients using propylthiouracil	3	0	N/A
Number of patients using methylprednisolone	1	3	0.305
Dose of methylprednisolone (mg/day)	18±2.8	28±7.3	0.490
Duration of methylprednisolone used (months)	6.5±2.1	7.5±2.3	0.870

AIT: Amiodarone-induced thyrotoxicosis, anti-Tg: Anti-thyroglobulin, anti-TPO: Anti-thyroid peroxidase, F: Female, M: Male, RAIU: Radioactive iodine uptake, TRAb: Thyrothyropine receptor antibody, TSH: Thyroid stimulating hormone, USG: Ultrasonography, *: p <0.05

(range:0-4), respectively. The median time to euthyroidism was nine months (range=5-12), the median thyroid volume was 13 cm^3 (range=7-20), and the initial 24-hour urinary iodine excretion was 1042 µg/day. The percentages of the 1st, 2nd, and 24th-hour RAIU were 2.5% (range=1.3-16), 2.4% (range=1.4-19), and 3% (range=1.2-28), respectively. Of the patients, 50% used methylprednisolone with a median dose of 32 mg (range=16-40) and with a median duration of 11 months (range=2-12), while 66.7% used methimazole with a median dose of 20 mg (range=20-25) and with a duration of 12.5 months (range:2-36).

DISCUSSION

Amiodarone is one of the most commonly used drugs for severe arrhythmias; however, it can cause amiodarone-induced thyroid dysfunction which affects morbidity and mortality rates.

In iodine-deficient regions, AIT was more frequent compared to hypothyroidism (22). The incidence of AIT was found to be high in Cape Town despite normal iodine exposure (23). It may be associated with different factors

other than iodine exposure (24). Although our country is a moderate to severe iodine-deficient region, we have no data about the prevalence of AIT.

Amiodarone-induced thyrotoxicosis is classified into type 1, where iodine uptake is increased/normal, and type 2, where iodine uptake is absent/very low (<2%); however, this distinction is not easy. Furthermore, due to the critical condition of the patient, it may not be possible to apply all diagnostic methods in the classification of AIT types. Also, during the follow-up period, it can be understood that the AIT classification made in the initial evaluation is incorrect. Amiodarone induced thyrotoxicosis is a difficult subject for many endocrinologists, and they may not have enough experience about its management. Raghavan RP et al. conducted an e-mail survey in the United Kingdom among endocrinologists on the management of AIT (25). The mean number of the cases examined in the last year by the physicians who completed the survey was 2.5. It was observed that 80% of the physicians used Anti-TPO, and 83% used the presence of goiter to differentiate between the type 1 and 2 AIT. The frequencies of the diagnostic methods used were 35% for RAIU, 35% for technetium scintigraphy, 34% for colored Doppler USG, 3.7% for serum interleukin-6, and 1.5% for urinary iodine excretion.

The number of patients in our study was 25 in two years, the main diagnostic test to differentiate the type of AIT was Anti-TPO (88%). Doppler USG was used in 52%, TRab in 44%, RAIU in 44%, thyroid USG in 36%, and urinary iodine excretion in 36%. We did not use interleukin-6 concentration. Detecting the presence of thyroid antibodies is an easy and a quick way, but mostly it is not enough to diferentiate the types of AITs.

For the initial treatment of type 1 AIT, 74% of the patients used thionamides alone, while 5.7% used thionamidesin combination with glucocorticoids in the study of Raghavan RP et al. These rates were lower than the ones in the European Thyroid Association (ETA) study. The "wait and see" approach, which was determined as 1% in the ETA study, was 6% in this study, and the difference between the rates of potassium perchlorate and thionamides combination (1.9% vs. 31%) was noteworthy (26). In the treatment of type 2 AIT, 30.8% of the patients used only glucocorticoids, and 35.6% used glucocorticoids combined with thionamides. Interestingly, 25% reported that they would use thionamides alone. However, it is known that the response to glucocorticoid treatment is better, and the symptoms improve faster in type 2 AIT (25). It can be said that the annual number of AIT cases examined by the physicians participating the study conducted in the United Kingdom was low, and the frequencies of potassium perchlorate use in type 1 AIT and glucocorticoid use in type 2 AIT were less than expected. In our study which represents a single-center approach to the management of AITs, 48% of the patients had type 1 AIT and 28% had type 2 AIT. The remaining 6 cases (24%) were classified as mixed-type AIT. In a study involving 20 patients reported from our country, 12 patients were reported to have type 1 AIT (60%), and six patients (40%) had type 2 AIT (27). Although these results are similar to these of our study, mixed-type cases also had an important place in our series.

In the present study, thionamides were used in all patients with type 1 AIT and in 57.1% of patients with type 2 AIT, while glucocorticoids were used in 28% of the patients overall. Erdoğan MF et al. evaluated the place of the stepwise approach in the treatment of AIT. Twenty patients were initially given 30-50 mg/day methimazole and 1000 mg/day potassium perchlorate for one month, and 12 patients (7-type 1 and 5-type 2) showed a significant decrease in thyroid hormones or euthyroidism. In the patients with inadequate response, 40-48 mg/day prednisolone was added in the second step, and euthyroidism was achieved in all of them. In that study, it was reported that initial classification may lead to unnecessary glucocorticoid administration, and stepwise treatment may be a good option. Also, they suggested that methimazole, potassium perchlorate, and prednisolone could be started together in severe cases (27).

In our study, one patient had a known history of multinodular goiter, and 10 patients had a nodular goiter on ultrasonographic evaluation. Increased frequency of nodules may be associated with iodine deficiency.

Radioactive iodine uptake at the 1st, 2nd, and 24th hour were measured in 11 (44%) of the patients. The 2nd hour measurement was compatible with the 24th hour measurement, and it was also a guide for AIT classification. In this context, our findings indicated that the 2nd hour RAIU measurement may be sufficient to determine a rapid treatment plan especially in severe patients.

Initial urinary iodine levels were evaluated in 17 (68%) patients. Eight of these patients had type 1 AIT, five had type 2 AIT, and four had mixed-type AIT. In our study, although initial urinary iodine level was lower in the patients with type 1 AIT than in the ones with type 2 AIT, the daily iodine excretion of both groups was >500 µg/L, indicating severe iodine exposure.

Generally, methylprednisolone 30 mg/day (or equivalent glucocorticoid) as initial therapy, and dose reduction with clinical improvement is recommended (28). In our study group, 28±7.3 mg/day prednisolone was used in type 2 AIT patients for 7.5±2.3 months. Because of the limiting effect of thyroid follicle cells destruction, recovery period of thyrotoxicosis was shorter in the patients with type 2 AIT. These findings were compatible with the literature (28).

Prophylactic thionamide to prevent the recurrence of type 1 AIT and the preparation for emergent thyroidectomy has rarely been reported in the literature. There is insufficient data to prove its efficacy and safety (29), and this method was not used in our study group.

Sodium perchlorate (NaCLO4) is a hard-to-reach treatment modality and has significant side effects, such as bone marrow suppression. Perchlorate was used in six patients at a dose of 300 mg thrice a day for 3 (1-6) months. Although it is not recommended to be used for longer than six weeks due to the risk of agranulocytosis, we needed to use perchlorate for a longer period in two patients because of the severity of thyrotoxicosis with blood cell counts checked every two weeks, and no adverse effect was noted. Seven patients received glucocorticoids and one patient developed severe osteoporosis resulting in vertebral fracture. Methimazole treatment was discontinued in a patient due to the absolute neutropenia (0/μL), and granulocyte colony-stimulating factor (G-CSF) was administered 30 mIU/day for four days. The neutropenia resolved on day five. One patient developed thrombocytopenia. The patients who experienced haematological adverse events did not receive any perchlorate treatment.

Radioactive iodine ablation therapy was administered as a radical treatment in three patients who developed complications related to the treatments, and levothyroxine replacement therapy was started after hypothyroidism was achieved.

There is no clear consensus on the discontinuation of amiodarone therapy. Arrhythmias can lead to serious complications in patients with AIT. Amiodarone is a potent antiarrhythmic, and the potential to worsen heart failure due to the negative inotropic side effects of other antiarrhythmics makes discontinuation difficult (30). On the other hand, some protective effects of amiodarone, such as its inhibitory effect on beta-adrenergic receptors, the inhibition of T4 deiodination and the blocking effects of T3 binding to thyroid receptors disappear with the discontinuation of the drug. However, it has been reported that early discontinuation would not be beneficial due to its long half-life (31). The decision to continue amiodarone should be based on cardiac findings, independent of thyroid hormone levels. In our study, amiodarone was continued in 6 (24%) patients. However, there was no information about the increase of arrhythmias in patients who discontinued the drug in the early period.

In our case group, RAI was preferred in 5 (20%) patients, and thyroidectomy was preferred in 1(4%) as radical solutions. Radioactive iodine treatment is not possible in the early period due to iodine contamination and low RAIU. If amiodarone can be discontinued, RAI treatment should be administered approximately 6-12 months later when the urinary iodine level normalizes and the RAIU reaches a sufficient level.

The new ETA guideline does not recommend the use of recombinant TSH (rhTSH) as it may increase the risk of exaggerated T4 increase and thus arrhythmia risk (28). However, our cases were managed before the publication of this guideline. Thus, with a single dose of rhTSH 0.9 mg/mL intramuscularly, FT4 concentration was increased 49 pmol/L to 100 pmol/L. The patient did not experience any cardiac deterioration or life-threatening arrhythmia during this period, and developed hypothyroidism in the 4th month of the treatment. It should also be kept in mind that some patients with low/absent RAIU values in the initial evaluations may have increased iodine intake during the follow-up and may have become eligible for RAI treatment.

According to the ETA guideline, thyroidectomy is currently the best option for rapid restoration of euthyroidism (28). However, in our series, only one patient underwent thyroidectomy, and we were inferior to the literature. Thyroidectomy is recommended without delay in AIT patients with impaired cardiac function or severe underlying cardiac disease and in patients whose thyrotoxicosis does not respond to medical therapies. It may be considered especially in type 1 AIT patients who have to continue amiodarone, have an autonomous thyroid gland, and in type 2 AIT patients with a high probability of relapse; however, preparation with glucocorticoids, β-blockers or plasmapheresis should be performed immediately before the surgery. We did not perform salvage thyroidectomy. Preferring RAI treatment more than thyroidectomy is probably associated with our conservative approach.

The present study had several limitations. We used retrospective records, which are not considered to be the best data sources. The sample size was not large enough. Due to the cross-sectional nature of the study, we could not establish causality by design, but could only describe relationships. Another limitation was that the results could not be generalized to the whole country, given the differences between regions and iodine replacement/depletion characteristics. Furthermore, it was clinically difficult to distinguish between the AIT types; for example, a pre-existing inflammatory process in the thyroid tissue makes typing increasingly difficult and is misinterpreted as mixed thyrotoxicosis. On the other hand, there were a limited number of studies on AIT in our country (27, 32). The numbers of patients in these studies were 20 and 4. In this regard, we consider that our study will contribute to filling the gaps in the literature. Furthermore, the comprehensive assessment performed in the present study was noteworthy. Our study was conducted in the largest metropolis in the country, and therefore, we believe that our study will elucidate the gaps about the management of AITs.

CONCLUSION

The management of AITs is difficult. Amiodarone-induced thyroid dysfunctions require the cooperation of endocrinologists and cardiologists. It is a fact that studies evaluating the awareness of cardiologists are also needed. An awareness questionnaire could be planned for patients using amiodarone to ask whether thyroid functions and thyroid antibodies are evaluated before starting treatment, how often thyroid functions are checked under treatment, and whether they refer to an endocrinologist when a problem is detected. Multicenter studies are needed in our country to determine the diagnostic tools, treatment approaches. It should be kept in mind that these patients may need amiodarone again; therefore, ablative treatments should be planned if needed.

Ethics Committee Approval: This study was approved by the Istanbul Faculty of Medicine Clinical Research Ethics Committee (Date: 26.05.2017, No: 10).

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EPIDEMIOLOGICAL AND CLINICAL CHARACTERISTICS OF HIDRADENITIS SUPPURATIVA PATIENTS: 10-YEAR EXPERIENCE FROM A SINGLE TERTIARY CENTER

HİDRADENİTİS SÜPÜRATİVA HASTALARININ EPİDEMİYOLOJİK VE KLİNİK ÖZELLİKLERİ: ÜÇÜNCÜ BASAMAK BİR MERKEZİN 10 YILLIK DENEYİMİ

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ABSTRACT

Objective: To investigate the clinico-epidemiological profile of hidradenitis suppurativa (HS) patients.

Material and Method: In this retrospective cross-sectional single tertiary center study, the HS patients diagnosed and/or followed up between 2012-2022 were evaluated regarding demographic features, clinical findings, associated comorbidities, therapies initiated for HS and their outcomes.

Results: Of 101 HS patients (male:female ratio=1.7:1), 23.3% (n=20) had a history of early-onset disease (<18 years). The majority had no family history of HS (82.7%, n=62). The patients were classified according to disease severity as Hurley I (33.7%, n=34), Hurley II (46.5%, n=47) and Hurley III (19.8%, n=20). Patients with early-onset disease and Hurley III HS had a significantly higher number of affected anatomical sites (p<0.05). The axillary region was the most commonly involved anatomical site (n=78), followed by the inguinal (n=57) and gluteal regions (n=23). Sixty-four patients (74.4%) were overweight/obese, and 84.5% (n=71) were current or ex-smokers. Acne vulgaris was the main dermatological comorbidity associated with HS (n=23). Pilonidal sinus disease was present in 25.5% (n=25). Patients with Hurley III HS presented with significantly higher rates of pilonidal sinus disease and involvement of the gluteal and perianal regions (p<0.05). Nineteen patients were diagnosed with metabolic syndrome. Systemic antibiotics were the most frequently prescribed first-line agents. Hidradenitis Suppurativa Clinical Response (HiSCR) achievement was observed most frequently with biologics, particularly adalimumab.

ÖZET

Amaç: Bu çalışmada hidradenitis süpürativa (HS) hastalarının epidemiyolojik ve klinik özelliklerinin araştırılması amaçlanmıştır.

Gereç ve Yöntem: Üçüncü basamak bir merkezde yürütülen bu retrospektif kesitsel çalışmada, 2012-2022 tarihlerinde tanı alan ve/veya takip edilen HS hastaları demografik özellikler, klinik bulgular, eşlik eden komorbiditeler, HS için verilen tedaviler ve tedavi yanıtları açısından değerlendirilmiştir.

Bulgular: 101 HS hastasının (erkek:kadın oranı=1,7:1) %23,3'ünde (n=20) erken başlangıç (<18 yaş) öyküsü mevcuttu. Hastaların büyük çoğunluğunda (%82,7; n=62) ailede HS öyküsü yoktu. Hastaların hastalık şiddetine göre dağılımları Hurley I (%33,7; n=34), Hurley II (%46,5; n=47), Hurley III (%19,8; n=20) şeklindeydi. Erken başlangıçlı ve Hurley III HS hastalarında anlamlı ölçüde daha fazla anatomik bölge tutulumu saptandı (p<0,05). En sık tutulum görülen anatomik yerleşim aksiller bölge (n=78) olup, bunu inguinal (n=57) ve gluteal bölge (n=23) takip etmekteydi. Altmışdört hasta (%74,4) kilolu/obez olup hastaların %84,5'inde (n=71) güncel/geçmiş sigara kullanım öyküsü mevcuttu. HS'e en sık eşlik eden dermatolojik hastalık akne vulgaristi (n=23). Olguların %25,5'inde (n=25) pilonidal sinüs hastalığı mevcuttu. Hurley III HS hastaları önemli ölçüde daha yüksek oranda pilonidal sinüs hastalığı, gluteal ve perianal bölge tutulumu ile başvurdu (p<0,05). Ondokuz hasta metabolik sendrom tanısı almıştı. Sistemik antibiyotikler en sık reçete edilen birinci basamak ajanlardı. Hidradenitis Süpürativa Klinik Yanıtı (HiSCR) en yüksek oranda biyolojik ajanlarla (özellikle adalimumab) gözlendi.

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Conclusion: In line with the current literature, HS poses an increased disease burden with its associated comorbidities. The predominance of the male sex and the anatomical involvement patterns seen in our HS patients are compatible with previously reported Turkish series. Pilonidal sinus disease and involvement of the gluteal and perianal regions in HS patients are important signs of severe disease, also highlighted in recent studies. The biologic agents seem to be the best therapeutic option for achieving HiSCR, especially in severe HS forms.

Keywords: Hidradenitis suppurativa, Hurley, chronic inflammation, metabolic syndrome, pilonidal sinus

Sonuç: Mevcut literatür ile uyumlu olarak, HS ilişkili olduğu komorbiditeler ile birlikte hastalık yükünü arttırmaktadır. HS hastalarımızda erkek cinsiyet baskınlığı ve anatomik tutulum paternleri daha önce bildirilen Türk serileri ile uyumludur. Pilonidal sinüs hastalığı, gluteal ve perianal bölge tutulumu HS hastalarında şiddetli hastalık açısından yakın zamanlı çalışmalarda da vurgulanan önemli belirtilerdir. Biyolojik ajanlar, özellikle şiddetli HS formlarında, HiSCR sağlamak için en iyi tedavi seçeneği olarak görünmektedir.

Anahtar Kelimeler: Hidradenitis süpürativa, Hurley, kronik inflamasyon, metabolik sendrom, pilonidal sinüs

INTRODUCTION

Hidradenitis suppurativa (HS) is a chronic inflammatory disorder of the hair follicle, presenting with recurrent deep-seated inflammatory nodules, sinus tracts, and disfiguring scars (1). The disease primarily affects intertriginous areas such as the axillary and inguinal folds and the anogenital region, where apocrine glands are abundant (2-4). Both genetic background and environmental factors have been incriminated in the emergence and course of the disease (5). The usual age of onset is between 20-30 years, mainly following puberty (2). The chronic, relapsing course significantly impacts the patient's quality of life (6) despite several therapeutic options emerging in the last decades (7).

HS has also been associated with comorbidities such as obesity, metabolic syndrome, cardiovascular disorders, tobacco smoking, mood disorders, polycystic ovary syndrome, inflammatory bowel disease, and spondyloarthropathies, necessitating a thorough evaluation to avoid further morbidity and mortality (8). In recent years, numerous papers have been published on the demographic and clinical profile of HS patients with diverse results (9).

The aim of this study is to investigate Turkish HS patients in terms of demographic and clinical characteristics, associated comorbidities and treatment results.

MATERIAL and METHODS

This was a retrospective cross-sectional single-center study on HS patients diagnosed based on the clinical findings and/or followed-up in a tertiary dermatology outpatient clinic between 2012-2022. The patients' medical files were evaluated regarding demographic features (age of presentation, sex), medical history (smoking, comorbidities), family history of HS, clinical findings [body mass index (BMI), duration of disease, age of disease onset, affected anatomical localization, disease severity], therapies administered for HS and treatment responses. Hurley staging system was used for the classification of disease severity based on the presence and degree of scarring and sinus tract formation as: mild (Hurley I), moderate (Hurley II), and severe (Hurley III) (10). The treatment response was evaluated with Hidradenitis Suppurativa Clinical Response (HiSCR) (11). HiSCR achievement was defined as at least a 50% reduction in the total number of abscess/inflammatory nodules, with no increase in abscess and draining fistula count compared to baseline.

Factors affecting the disease severity and differences among male/female sex were further assessed. The presence of family history was accepted if the disease was present in a first or second-degree relative. Early-onset disease was accepted as the age of onset <18 years. The BMI was categorized as normal weight (BMI<25 kg/m2), overweight (25-29.9 kg/m2), and obese (≥30 kg/m2).

The study was approved by the institutional ethical committee (Date: 16.11.2022, No: 2022/14-27) and conducted in accordance with the Declaration of Helsinki.

Statistical analysis

IBM SPSS Statistics Version 28.0 was used to store and analyze the data. Descriptive statistics were calculated as mean, standard deviation, median, minimum, and maximum values for continuous variables, and as frequency and percentage for categorical variables. The distribution of variables was measured with the Kolmogorov-Smirnov test. Kruskal-Wallis and Mann-Whitney U tests were used to analyze independent quantitative data. The chi-squared test or Fisher's exact test was used for comparing categorical variables between groups. The p-value less than 0.05 was considered statistically significant. The patients with missing information were excluded during the statistical evaluation of the related data.

RESULTS

A total of 101 patients were evaluated with the diagnosis of HS. Of these, 50 presented to the outpatient clinic only once, and 51 were followed up for a median of nine

months (range:1-144 months). The demographic and clinical characteristics of the patients are summarized in Table 1. The male:female ratio was 1.7:1. There was a history of early-onset disease (<18 years) in 20 patients (23.3%). The majority of the patients (82.7%, n=62) denied any history of HS in other family members. There was no significant difference among patients with early and adult-onset disease in terms of family history.

The classification of patients regarding disease severity was as follows; Hurley I (33.7%, n=34), Hurley II (46.5%, n=47) and Hurley III (19.8%, n=20). The distribution of disease severity showed no significant difference in terms of sex, age of onset or BMI, while the disease duration was significantly longer in Hurley stages II and III compared to Hurley I ($p<0.05$) (Table 2).

More than one anatomical site was involved in 65 patients. The patients with early-onset disease had a significantly higher mean number of affected anatomical sites (2.6±1.1) compared to those with adult-onset disease (2.0±1.0) ($p<0.05$). Similarly, the patients with Hurley III HS had a higher number of regions involved compared to ones with Hurley I and Hurley II ($p<0.05$) (Table 2).

The axillary region was the most commonly involved anatomical region (n=78), with significant predominance in males [male 90.5% (n=57) vs. female 56.8% (n=21); $p<0.05$]. Inguinal (n=57) and gluteal region (n=23) were the second and third most frequent localizations, the latter being more significantly involved in patients with early-onset disease [early-onset 45.0% (n=9) vs. adult-onset 16.7% (n=11); $p<0.05$]. The patients with Hurley III disease presented with significantly higher rates of gluteal and perianal region involvement and pilonidal sinus disease ($p<0.05$) (Table 2). The inframammary region was affected more frequently in females compared to males [female 40.5% (n=15) vs. male 0% (n=0); $p<0.05$].

Pilonidal sinus disease was present in 25.5% (n=25), with a significantly higher rate in males [male 36.5% (n=23) vs. female 5.7% (n=2); $p<0.05$]. Acne vulgaris was the main dermatological comorbidity associated with HS (n=23). Of these, four patients had acne conglobata, and two

Table 1: Demographic and clinical characteristics of 101 hidradenitis suppurativa patients

Sex (male:female)	64:37 (1.7:1)
Age of disease onset (years)	12-64 (median:23)
Age of disease onset category n (%)	
Early (<18 years)	20 (23.3)
Adults (≥18 years)	66 (76.7)
Missing data	15
Age at presentation (years)	14-66 (median:30)
Family history of HS n (%)	
Present	13 (17.3)
Not present	62 (82.7)
Missing data	26
Duration of disease prior to presentation n (%)	6 months-33 years (median: 4.5 years)
<5 years	43 (50)
5-10 years	18 (20.9)
>10 years	25 (29.1)
Missing data	15
BMI (mean±SD)	28.9±6.0
BMI classification n (%)	
Normal	22 (25.6)
Overweight	30 (34.9)
Obese	34 (39.5)
Missing data	15
Smoking n (%)	
Current/ex-smoker	71 (84.5)
Never	13 (15.5)
Missing data	17

Table 1: Continue

Comorbidity (n)	
Acne	23
Hyperlipidemia	21
Metabolic syndrome	19
Diabetes mellitus	16
Hypertension	13
Mood disorders	11
Thyroid disorders	6
Hirsutism	5
Polycyctic ovary syndrome	4
Crohn's disease	3
Dissecting cellulitis	2
Ankylosing spondylitis	1
Associated acne subtype (n)	
Mild	12
Moderate-severe	7
Acne conglobata	4
Pilonidal sinus disease n (%)	
Present	25 (25.5)
Not present	73 (74.5)
Missing data	3
Disease severity n (%)	
Hurley I	34 (33.7)
Hurley II	47 (46.5)
Hurley III	20 (19.8)
Affected anatomical site (mean±SD)	1-5 (2.1±1.1)
Affected anatomical site n (%)	
1	35 (35)
≥2	65 (65)
Missing data	1
Disease localization (n)	
Axilla	78
Inguinal	57
Gluteal	23
Genital	16
Inframammary	15
Perianal	8
Other	9

BMI: Body mass index, HS: Hidradenitis suppurativa, SD: Standard deviation

had dissecting cellulitis, while one of them was diagnosed with follicular occlusion tetrad.

When patients were classified regarding BMI, 64 patients (74.4%) were observed to be above the normal range. Seventy-one patients (84.5%) were current or ex-smokers. Nineteen patients fulfilled the diagnostic criteria for metabolic syndrome. Three patients were diagnosed with Crohn's disease, whereas one had ankylosing spondylitis. Five female patients had hirsutism, and four had a diagnosis of polycystic ovary syndrome. Mood disorder diagnosis had been established in eleven patients.

Medical treatment was administered in the majority of the patients (n=91), while surgery was the treatment of choice only in six patients. Topical clindamycin was the most commonly prescribed topical medication (n=72), mainly in combination with a systemic agent (n=66). The

Table 2: Distribution of demographic and clinical findings of hidradenitis suppurativa patients regarding Hurley staging

			Hurley- I	Hurley- II	Hurley- III	p-value	
Age of disease onset (years)		mean±SD	25.0±10.6	25.4±10.6	25.2±10.6	0.974	K
		median	22.0	23.0	23.0		
Age of disease onset	Early-onset	n-%	7 23.3%	8 21.6%	5 22.7%	0.925	X^2
	Adult-onset	n-%	23 76.7%	29 78.4%	17 77.3%		
Gender	Female	n-%	13 38.2%	20 42.6%	4 20.0%	0.209	X^2
	Male	n-%	21 61.8%	27 57.4%	16 80.0%		
BMI		mean±SD	29.5±6.0	28.7±6.1	28.3 ±6.1	0.801	K
		median	29.0	27.8	28.3		
Duration of disease prior to presentation (years)		mean±SD	5.0±6.2	8.4±8.0	8.8±7.7	***0.017***	K
		median	2.5	5.0	8.0		
Smoking (yes)		n-%	19 70.4%	37 92.5%	15 88.2%	***0.044***	X^2
Metabolic syndrome		n-%	9 28.1%	7 15.9%	3 15.0%	0.349	X^2
Diabetes mellitus		n-%	8 25.0%	6 12.8%	2 10.0%	0.246	X^2
Hypertension		n-%	4 12.5%	6 13.0%	3 15.0%	0.965	X^2
Hyperlipidemia		n-%	7 21.9%	10 21.7%	4 20.0%	0.985	X^2
Mood disorders		n-%	4 12.1%	3 6.5%	4 20.0%	0.270	X^2
Family history of HS	Not present	n-%	23 88.5%	25 73.5%	14 93.3%	0.151	X^2
	Present	n-%	3 11.5%	9 26.5%	1 6.7%		
Affected anatomical site		mean±SD	1.7±0.9	2.0±0.9	2.8± 1.2	***0.004***	K
		median	1.0	2.0	2.5		
Pilonidal sinus disease (present)		n-%	7 21.9%	8 17.4%	10 50.0%	***0.017***	X^2
Axilla		n-%	26 76.5%	37 80.4%	15 75.0%	0.856	X^2
Inguinal		n-%	14 41.2%	29 63.0%	14 70.0%	0.063	X^2
Gluteal		n-%	6 17.6%	7 15.2%	10 50.0%	***0.006***	X^2
Inframammary		n-%	5 14.7%	7 15.2%	3 15.0%	0.998	X^2
Genital		n-%	4 11.8%	7 15.2%	5 25.0%	0.432	X^2
Perianal		n-%	0 0.0%	2 4.3%	6 30.0%	**<0.05**	X^2
Other		n-%	3 8.8%	4 8.7%	2 10.0%	>0.05	X^2

BMI: Body mass index, HS: Hidradenitis suppurativa, SD: Standard deviation, K: Kruskal-wallis (Mann-whitney u test), X^2: Chi-squared test

systemic medications and their treatment responses are summarized in Table 3. Systemic antibiotics, namely doxycycline and rifampicin-clindamycin combination, were the first-line agents used for disease control for 1-3 months. In the case of past clinical response, the regimens were used more than once for a flare in seven and two patients, respectively. The use of retinoids was beneficial in eight patients.

Biologics were initiated mainly in Hurley III patients resistant to systemic antibiotics. HiSCR achievement was observed most frequently with biologics, particularly adalimumab, and the treatments were used for a period of 6 months to a maximum of 21 months (Figure 1). Secondary loss of efficacy was encountered in two patients with adalimumab after 14 months and 21 months, respectively. Thus, a switch to infliximab was performed, resulting in HiSCR in three months.

In 14 patients, nodular lesions were managed with intralesional corticosteroid injection once a month, promoting a temporary achievement in nine patients. After excisional surgery, complete healing was observed in two patients (one with Hurley II axillary and one with Hurley III gluteal HS).

DISCUSSION

The literature on HS has evolved particularly through the last two decades with epidemiological studies and clinical trials on therapeutic options. In light of the growing body of information, the awareness of the impact of HS on quality of life and its association with systemic disorders has increased globally (12). Although not well-established, the HS prevalence was reported to range between 0.00033-4.1% (1). There is an inconsistency regarding sex predilection among studies from different geographical regions. Female predominance was present in Western Europe and American studies, while males were reported to be affected more frequently in Turkey and Asian countries (9,12-15). Ethnicity was asserted as a possible factor for this difference (16). A recent multicentric study conducted on 1221 HS patients from Turkey has demonstrated the male sex as one of the main risk factors for the disease severity. The authors attributed the male predominance in the Turkish population to the possible increased admission of male patients to healthcare services due to the greater severity of the disease (13). On the other hand, there was no significant difference between males and females regarding disease severity in our study.

Family history of HS was reported in approximately one-third of the European patient population, whereas this rate was extremely lower in Asian studies (0.07-4%) (15). The presence of family history was associated with an earlier median/mean age of disease onset in several reports (6,17). Furthermore, two European studies comparing characteristics of patients with early-onset (onset before the age of 13 or 18) and normal/adult-onset HS revealed an association between early-onset disease and a positive family history of HS (2,18). The family history (in 17.3% of our patients) was not shown to impact our HS patients regarding the age of onset. However, a significantly higher number of anatomical regions were affected in patients with an early-onset disease with no impact on Hurley stage distribution, similar to the findings of one of the studies mentioned above (18).

Consistent with recent Turkish studies, in our series most frequently involved anatomical sites were observed as axillary and inguinal regions, respectively (9,13,14). Data from European and North American patient populations also showed these locations as the main involved areas (17,19,20). In contrast, there was a predilection of gluteal region involvement in Asian cohorts (21,22). French researchers indicated a predominant involvement of the front part of the body (inguinal and mammary) in females

Table 3: Systemic treatment modalities administered in hidradenitis suppurativa patients

Treatment option	Number of patients n (%)	Patients lost to follow-up	Treatment response	Side effect (n)
Doxycycline	47 (46.5)	25	HiSCR in 8 patients (36.4%)	Gastrointestinal intolerance (1)
Rifampicin+clindamycin	36 (35.6)	21	HiSCR in 8 patients (53.3%)	Diarrhea (1)
Retinoids (acitretin/isotretinoin)	25 (24.8)	3	HiSCR in 8 patients (36.4%)	Hyperlipidemia (1)
Adalimumab	15 (14.9)	3	HiSCR in 8 patients (66.7%)	None
Infliximab	2 (1.9)	0	HiSCR in 2 patients (100%)	None

HiSCR: Hidradenitis Suppurativa Clinical Response

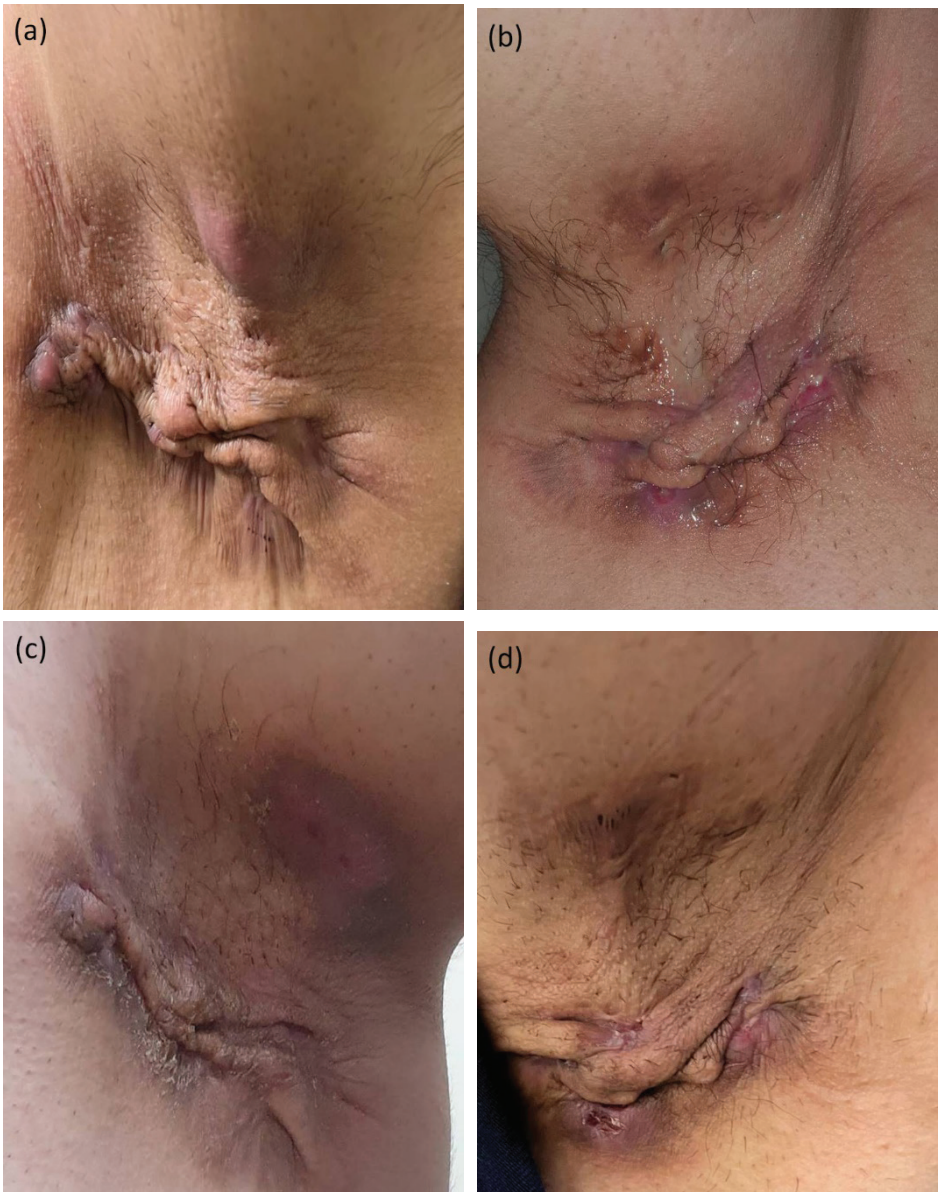

Figure 1: (a) and (b) Inflammatory nodules and sinus tracts in the axillary regions of hidradenitis suppurativa patients. (c) and (d) Hidradenitis Suppurativa Clinical Response (HiSCR) achievement in patients following six months of adalimumab treatment.

and the back part (gluteal and perianal) in males (6). Likewise, a significantly higher rate of inframammary region involvement was detected in our female patients. A similar predilection was demonstrated in different Turkish studies (13,14).

The factors associated with disease severity were frequently discussed in previous reports. Male sex, extended duration of disease and obesity/increased BMI were presented as the leading risk factors in the literature (9,13,17,19,23,24). No significant impact of sex or BMI was detected on the distribution of Hurley staging in our study, while a significantly longer disease duration was observed in the patients with Hurley II and III HS compared to Hurley I. Correspondingly, a multicenter study revealed an average diagnostic delay of 7.2 years for HS patients and an increased likelihood of late admission in patients with moderate-to-severe disease (25). The window of opportunity is a term used to define the early disease period prior to the formation of irreversible HS lesions such as fistulas, sinus tracts and scarring (26). A recent study demonstrated a negative correlation between the therapeutic delay and response to biologic therapy. The authors stated that early drug administration during the window of opportunity phase would achieve better disease control (26). Our findings regarding the extended

disease duration in moderate-to-severe HS patients also support the prompt intervention strategy during the early disease phase to prevent further progression.

The number of affected anatomical sites was detected to be higher in our patients with Hurley III HS. This was a significant finding also encountered in a series from Lithuania (3). A Korean study also mentioned that HS severity was associated with the involvement of ≥2 body regions (21). Moreover, the gluteal and perianal region involvement rates were significantly higher in our patients with Hurley III disease. Similarly, perianal involvement was detected as one of the strongest severity risk factors in a series from the Netherlands (17), in addition to another study from Switzerland demonstrating a significant association between lesions in the gluteal/perianal regions and higher Hurley stages (19).

The association of HS with other dermatological disorders with a common pathogenetic mechanism characterized by follicular occlusion, namely acne conglobata and dissecting cellulitis of the scalp, was described in the literature. These conditions comprise a follicular occlusion triad together with HS. When the pilonidal sinus disease coexists with this group of lesions, the clinical diagnosis is named follicular occlusion tetrad (27).

Pilonidal sinus disease was one of the most commonly associated comorbidities in HS patients, with a rate of 4.6-30% reported in the literature (28). Some authors considered pilonidal sinus disease as part of the HS disease spectrum (29). The 25.5% rate of pilonidal sinus disease observed in our series was compatible with these results and similar to the rate detected in the large series from Turkey (23.6%) (13). This rate was much higher than the prevalence of pilonidal sinus disease reported in the healthy Turkish population (6.6%) (30). Some authors described a significant predilection in males, as in our study (6,16). Furthermore, pilonidal sinus disease was found to be significantly more frequent in our patients with Hurley III HS. Similarly, Kimball et al. reported an over four-fold increased prevalence of pilonidal sinus disease in more severe HS forms compared to mild disease (31). Benhadou et al. described a significant rate of severe HS in patients with inflammatory lesions localized in the intergluteal fold. In that study, the authors further classified those lesions in the intergluteal fold. They identified pilonidal sinus disease in 78% of these patients, while pointing out that the rest had true HS lesions rather than pilonidal sinus disease (28). Such discrimination was not possible due to the retrospective nature of our study.

HS has been associated with several systemic comorbidities in which systemic inflammation plays a role. Metabolic syndrome and its components (diabetes mellitus, hypertension, hyperlipidemia and obesity) were detected to have a higher prevalence in HS patients compared to controls, with obesity being the most frequently associated condition (1,8). The majority of the patients with HS (50-75%) were reported to be overweight or obese, while high BMI was shown to be associated with severe disease (1). In contrast, no significant difference in the distribution of Hurley stages regarding BMI was established in our patients, despite 74.4% being above the normal BMI range. Besides metabolic comorbidities, inflammatory bowel disease (especially Crohn's disease), inflammatory arthritis, polycystic ovary syndrome and psychiatric disorders, which were also detected in our cohort, were associated with HS (1). Smoking is a modifiable factor strongly associated with HS (27). Nearly 85% of our HS patients had a current or previous history of smoking, a rate corresponding to the estimated prevalence of 70-90% in HS patients in the literature (1).

In line with the current treatment recommendations (10,32) and real-life data from different studies (13,14,33), anti-inflammatory antibiotics, particularly doxycycline, were the most frequently prescribed treatment options. In cases with severe HS, resistant to these treatments, adalimumab was the first biologic agent introduced in our series with HiSCR in more than half of the patients, the highest rate seen among the administered therapeutic options. Similarly, in a recent study from Turkey, 80% of moderate-to-severe HS patients achieved HiSCR with biologics (14).

The main limitations of our study were its retrospective design and the missing information about some patients. Moreover, there might be a recall bias regarding the age of disease onset as it was mainly gathered from patient history. The evaluation of the patients by the same observer group was its main strength.

CONCLUSION

HS is an inflammatory disorder with an increased disease burden. Clinicians should be aware of comorbidities associated with HS while evaluating their patients. The predominance of the male sex and the tendency for the involvement of axillary and inguinal regions in our HS patients further support the findings of previous Turkish reports (9,13,14). Pilonidal sinus disease and involvement of the gluteal and perianal regions in HS patients are important signs of severe disease, in line with recent studies (17,19,28,31). Despite the effectiveness of several anti-inflammatory antibiotics and retinoids, biologic agents seem to be the best therapeutic option to achieve HiSCR, especially in severe HS forms.

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THE KIDNEY AT RISK: UNDERSTANDING CRUSH SYNDROME-RELATED ACUTE KIDNEY INJURY

RİSK ALTINDAKİ BÖBREK: EZİLME SENDROMUNA BAĞLI AKUT BÖBREK HASARI

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ABSTRACT

Crush syndrome (systemic manifestations of traumatic rhabdomyolysis) is the second leading cause of death after earthquakes or other destructive disasters. Crush-related acute kidney injury (AKI) is the most important Component of crush syndrome, and medical professionals living in disaster-prone regions should know about its pathophysiology, clinical and laboratory features, complications, and treatment. Pathogenesis of AKI on the basis of crush injuries is multifaceted. The most important mechanism is compartment syndrome-related hypovolemia, and consequent renal hypoperfusion, which may result in ischemic acute tubular necrosis. Also, rhabdomyolysis-related myoglobinuria may result in the formation of kidney-damaging myoglobin casts and direct tubular toxicity. Formation of uric acid plugs, oxidant injury, increased serum levels of cytokines, and still many other factors may take a role in the pathogenesis as well. Crush syndrome can cause serious electrolyte imbalances, sepsis, and bleeding, which can further exacerbate AKI. Early recognition and appropriate management, which includes aggressive hydration and management of electrolyte imbalances can help to prevent or minimize kidney damage. This review provides an overview of the pathophysiology, complications, and treatment of AKI in the context of Crush syndrome.

Keywords: Crush syndrome, acute Kidney injury, rhabdomyolysis

ÖZET

Ezilme sendromu, depremler veya diğer yıkıcı afetlerde ölümün ikinci en yaygın nedenidir. Ezilmeyle ilişkili akut böbrek hasarı (ABH), ezilme sendromunun en önemli bileşenidir. Bu nedenle, sağlık profesyonellerinin patofizyoloji, klinik ve laboratuvar özellikleri, komplikasyonlar ve tedavi hakkında bilgi sahibi olmaları büyük öneme haizdir. Ezilme yaralanmalarına ikincil gelişen ABH'nin patogenezi çok yönlüdür. Kompartman sendromuna bağlı hipovolemi ve renal hipoperfüzyon, iskemik akut tübüler nekroza yol açabilen başlıca mekanizmadır. Ayrıca, miyoglobinüri miyoglobin tıkaçlarının ve doğrudan tübüler toksisitenin oluşumuna neden olabilir. Oksidatif hasar, artmış sitokin düzeyleri ve diğer faktörler de patogeneze katkıda bulunabilir. Ezilme sendromu, ciddi elektrolit dengesizlikleri, sepsis ve kanama gibi durumları tetikleyebilir ve bu durum ABH'yi daha da kötüleştirebilir. Erken tanı ve uygun tedavi, agresif hidrasyon ve elektrolit dengesinin yönetimi gibi faktörler, renal hasarı önlemeye veya en aza indirmeye yardımcı olabilir. Bu derleme, ezilme sendromu bağlamında ABH'nin patofizyolojisi, komplikasyonları ve tedavisi hakkında bir genel bakış sunmaktadır.

Anahtar Kelimeler: Ezilme sendromu, akut böbrek hasarı, rabdomiyoliz

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INTRODUCTION

Crush syndrome is the second most frequent cause of death after earthquakes and can lead to several complications, including acute kidney injury (AKI), sepsis, acute respiratory distress syndrome, bleeding, hypovolemic shock, cardiac failure, arrhythmias, electrolyte disturbances, and psychological trauma (1).

Crush-related AKI is a life-threatening complication of crush injuries that can occur after destructive natural disasters or man-made catastrophes. It is essential for medical professionals, especially those living in disaster-prone regions, to have knowledge about the pathophysiology, complications, and treatment of this condition.

Crush injuries can cause damage to the kidneys due to the compression of muscle tissues, leading to baromyopathy-related compartment syndrome, and rhabdomyolysis, a condition that results in the release of myoglobin into the bloodstream (2). These events can lead to hypovolemia, hypoperfusion of the kidneys, formation of kidney-damaging myoglobin casts, and finally AKI. In addition, traumatic rhabdomyolysis can cause electrolyte imbalances, sepsis, and bleeding, which can further exacerbate kidney injury (3-5).

Medical professionals should be aware of the signs and symptoms of crush-related AKI, including decreased urine output, elevated serum creatinine and blood urea nitrogen levels, and electrolyte imbalances. Early recognition and appropriate management, including aggressive hydration and management of electrolyte imbalances, can help prevent or minimize kidney damage.

This review focuses on the pathophysiology, complications, and treatment of AKI, which is a major component of Crush syndrome.

Definitions

"Crush injury" indicates a direct injury by collapsing material and debris causing manifest muscle swelling and/or neurological disturbances in the affected parts of the body. The injury to the soft tissues, muscles, and nerves can be a result of primary direct trauma and ischemia secondary to compression. A severe crush injury can lead to muscle necrosis (rhabdomyolysis) and subsequent complications.

Rhabdomyolysis refers to the destruction of striated muscle cells, resulting in the release of intracellular components into the bloodstream. This condition can arise from traumatic or non-traumatic causes and may result in a range of clinical and laboratory abnormalities. Nontraumatic rhabdomyolyis may develop on the basis of ischemic, genetic/metabolic, toxic, and oncologic factors (6). While various cutoff limits for serum creatine phosphokinase (CK) levels have been suggested for diagnosing rhabdomyolysis, generally, levels exceeding five times the upper limit of normal for a given local laboratory are considered indicative of the condition. The cutoff values have been proposed to range from 500 to 3000 U/L (7-9).

Crush syndrome is a pathological condition resulting from systemic manifestations of traumatic rhabdomyolysis. This condition is primarily caused by the compression of muscle tissue for a sustained period of time, leading to hypovolemia, muscle necrosis, and the release of various intracellular contents, such as myoglobin, potassium, uric acid, phosphorus, thromboplastin, nucleic acids, creatine, and creatinine phosphokinase. Hypovolemia and increased serum levels of these substances can have toxic effects on various organs and systems, leading to a range of systemic manifestations. The clinical manifestations of Crush syndrome include AKI, sepsis, acute respiratory distress syndrome (ARDS), disseminated intravascular coagulation (DIC), hypovolemic shock, cardiac failure, arrhythmias, and electrolyte disturbances (10).

Factors affecting AKI incidence in disaster victims

Crush syndrome occurs in 2-5% of victims of catastrophic earthquakes and 30-50% of traumatic rhabdomyolysis patients (11, 12). Pediatric patients have a lower risk of experiencing crush-related injury and mortality (12).

Acute kidney injury incidence in disaster victims is affected by various factors such as the severity of the disaster, population density of the affected area, quality of buildings, timing, and effectiveness of rescue efforts. The efficacy of rescue efforts is a crucial factor, as delayed or inefficient rescue efforts result in more deaths and fewer cases of AKI. Hence, disasters with similar intensity may result in marked differences in AKI numbers. For example, the incidence of AKI was almost four times higher in the Bam earthquake in Iran than in the Gujarat earthquake in India, despite both having approximately 20,000 deaths (13). The difference was explained by the daytime occurrence of the Gujarat disaster, thus instant deaths due to head trauma (14). The collapse of the Twin Towers in New York resulted in only one case of AKI despite more than 3000 deaths (15).

In some disasters, the need for dialysis was high. For instance, the Kobe earthquake had a dialysis requirement of 54%, and the Marmara earthquake had a dialysis requirement of 75% (16, 17). Dialysis was required in 6.5% of 1975 patients admitted to the hospital in the Bam earthquake, and the majority of victims were rescued in less than four hours, which might explain the lower rate of dialysis requirement compared with other reports (18). In the Kobe earthquake, the need for hemodialysis was directly correlated with increased serum creatine kinase levels (17). Therefore, the severity of traumatic rhabdomyolysis is a crucial factor in the development of AKI in disaster victims.

Earthquakes and acute kidney injury: Pathophysiological links

Pathophysiology of Crush syndrome can be considered under the headings of 1) Pathogenesis of traumatic rhabdomyolysis, and 2) pathogenesis of rhabdomyolysis-induced AKI as well as other systemic symptoms and signs of rhabdomyolysis (Crush syndrome) (2). Compression of the muscles (*baromyopathy*) is the initial event in traumatic rhabdomyolysis, which causes an increased permeability of sarcolemma (2). Consequently, substances abundant within the muscle cells (i.e. potassium, myoglobin, phosphate), move to the extracellular environment, while, sodium, chloride, water, and calcium diffuse into the cell, according to their electrochemical gradients, which results in cellular swelling (leading to "compartment syndrome") (19). Increased intracellular calcium activates proteolytic enzymes that cause lysis of the muscle fibers (rhabdomyolysis). Muscular ischemia on the basis of increased intramuscular pressure as well as ischemia-reperfusion injury, which develops during the rescue of the victims, contribute to the pathogenesis of muscle cell necrosis (20).

The details of these pathophysiological processes are as follows. After surpassing a critical threshold of free calcium concentration, persistent muscle contraction occurs, leading to the depletion of ATP reserves. This, in turn, triggers mitochondrial impairment, causing oxidative stress, and activating proteases, phospholipases, and other enzymes that cause damage to myofibrils and membrane phospholipids. The outcome is the breakdown of myocytes and the discharge of harmful intracellular components into the extracellular microenvironment. Local accumulation of these products causes microvasculature damage, producing capillary leak, subsequently causing the compartmental syndrome, which increases pressure on the capillaries triggering occlusion of the microcirculation and rapidly depleting myoglobin oxygen content. Similarly, creatine, phosphate, and glycogen stores are exhausted as well, and severe ATP depletion ensues (21). However, in ischemic tissue injury, most of the damage occurs after flow into the damaged tissue is restored. In this case, leukocytes migrate into these particular tissues after reperfusion has started, and the production of free radicals starts after oxygen is available (reperfusion injury). The localized accumulation of these substances leads to the impairment of microvascular structures, which causes capillary leakage and results in compartmental syndrome. As a result, pressure on the capillaries increases, leading to occlusion of the microcirculation and rapid depletion of myoglobin oxygen content. Likewise, creatine, phosphate, and glycogen stores become depleted, leading to severe ATP exhaustion. However, in tissue injury due to ischemia, the majority of the damage occurs after blood flow is restored to the affected area. In this situation, leukocytes migrate to the damaged tissues after reperfusion commences, and the generation of free radicals starts after the availability of oxygen (reperfusion injury) (22). In cases of limb injury or compression, intramuscular pressure can exceed 240 mm Hg, resulting in ischemia and potentially causing rhabdomyolysis. It is possible for compartment syndrome to occur independently and result in full-blown rhabdomyolysis, despite the presence of normal arterial pedal pulses and warm skin in patients with anterior tibial compartment syndrome (19).

The primary pathophysiological mechanisms involved in the development of AKI are hypovolemia-induced renal hypoperfusion, renal vasoconstriction, intraluminal cast formation, and direct cytotoxicity induced by myoglobin (23). Inflammation plays a crucial role in this process, as it triggers the storage of large amounts of body water in the muscle tissue, leading to limb swelling and compression of blood vessels and nerves, known as compartment syndrome. This inflammation also leads to severe hypovolemia, a major cause of AKI.

Decreased circulating calcium levels can lead to immediate negative cardiac inotropism and arrhythmias, further worsening kidney hypoperfusion contributing to AKI (7). Later, calcium may also induce tissue calcification (24).

One of the critical compounds released from muscle cells is potassium. Hyperkalemia, in combination with hypocalcemia, provokes arrhythmias and negative inotropism, making it pathophysiologically more devastating. High anion gap acidosis, further exacerbates hyperkalemia. Phosphorus release causes hyperphosphatemia, worsening of hypocalcemia, and leads to calcium-phosphorus deposits in the kidneys (6).

During rhabdomyolysis, large amounts of myoglobin are released from the muscle tissue and filtered by the glomeruli. This leads to tubular cast formation and obstruction, particularly in cases of hypovolemia, increasing the risk of AKI (25). The liver metabolizes myoglobin to bilirubin, which is also a nephrotoxic agent. Finally, nucleotide release causes hyperuricemia, which is another cause of cast formation and kidney damage (26).

In disaster situations, victims are at high risk of AKI due to various precipitating factors beyond rhabdomyolysis. These factors include bleeding, dehydration, sepsis, urinary tract obstruction, surgical interventions, and intoxication. In addition, the chaotic nature of emergency situations in disasters can lead to incompatible blood transfusions, which may cause further kidney damage (13).

Acute kidney injury in crush-related injuries: Causes and manifestations

AKI may range from mild to severe and can even require dialysis. The severity of AKI depends upon various factors such as the extent of muscle injury, degree of volume

depletion, presence or absence of underlying comorbid conditions, and the development of complications such as sepsis (5, 8). Similar to other types of AKI, crush-associated AKI can originate mainly from three distinct etiologies: prerenal, intrarenal, and postrenal.

Prerenal AKI can occur due to severe hypovolemia, which is common among victims of crush-related injuries. The loss of access to water while being trapped for hours or days leads to ongoing losses resulting in negative fluid balance. Vascular injury can cause bleeding leading to hypovolemic shock. Upon rescue, decompression at the sites of muscle injury can result in reperfusion-related third spacing of fluid leading to compartment syndrome, hypovolemia, and prerenal AKI (21).

Intrarenal AKI is typically caused by rhabdomyolysis. The characteristic manifestation of rhabdomyolysis-related acute tubular necrosis (ATN) is dark red, brown, or black urine. However, urine may not be discolored in some patients with rhabdomyolysis-related ATN if their urine is diluted from aggressive fluid resuscitation. Microscopic evaluation of the urinary sediment often reveals pigmented granular casts. AKI resulting from heme pigment-induced ATN is usually characterized by an initial oliguric period, followed by polyuria, which usually starts within one to three weeks after the primary event. Some cases may present with a non-oliguric course. Although not a general rule, the first stage of AKI following a crush injury is typically characterized by oliguria, which can last 7 to 21 days (27). Oliguric AKI is generally associated with a poor prognosis (5, 28). During the early oliguric phase of AKI following crush, patients are subject to more severe uremia and fluid-electrolyte disturbances.

Other causes of intrarenal AKI include ischemic or toxic injury from prolonged shock, sepsis, use of nephrotoxic agents, cardiac failure, arrhythmias, or transfusion reactions. Postrenal AKI may develop due to traumatic injury or obstruction of the urinary outflow tract, mostly in patients suffering from pelvic trauma.

Diagnostic markers and other metabolic abnormalities

Rhabdomyolysis is a condition characterized by the release of creatine kinase (CK) from damaged muscles into the circulation. This can result in a significant increase in serum CK levels, with levels peaking within 24 hours of injury and declining thereafter (29). While the degree of CK elevation does not always predict the development of AKI, there is a weak correlation between peak CK level and serum creatinine (23). Mildly elevated CK-MB levels may be seen in the absence of myocardial involvement. In addition to CK, peak plasma myoglobin levels may also correlate with AKI, but this test is less commonly used in clinical practice. CK levels can rise dramatically after muscle injury, but the degree of elevation does not always correlate with the development of AKI. Patients with peak CK levels >16,000 units/L are more likely to develop AKI, but AKI is uncommon when peak CK levels are under 5000 to 10,000 units/L (30). Myoglobin levels may correlate more closely with AKI than CK, but myoglobin levels may have resolved by the time the patient presents with AKI (31).

Abnormalities of serum calcium are common. Hypocalcemia can occur in up to two-thirds of patients, and it is due to the increase in serum phosphate and the subsequent deposition of calcium phosphate into injured muscle, as well as decreased bone responsiveness to parathyroid hormone (PTH). Hypercalcemia can occur during the recovery phase of rhabdomyolysis in up to 20 to 30% of patients (32, 33). This is due, in part, to the mobilization of calcium that has been deposited in the injured muscle.

Phosphate may also be elevated in patients with rhabdomyolysis, leading to hyperphosphatemia and a mild to moderate high anion gap acidosis (7).

Intra-myocyte enzymes, including AST, ALT, LDH, and aldolase, may also increase in patients with rhabdomyolysis. These may be the first biochemical abnormalities to be detected, and they are often initially misinterpreted as indicating liver disease.

Patients with rhabdomyolysis may exhibit hyperuricemia due to the discharge of nucleosides from impaired myocyte nuclei, leading to the synthesis of purines in the liver and their eventual conversion to uric acid. In severe cases of rhabdomyolysis, thromboplastin release from cells may cause the onset of disseminated intravascular coagulation (7).

Prevention

The importance of early and adequate fluid resuscitation to prevent AKI in patients with rhabdomyolysis due to crush injury is well established (34). Studies on fluid resuscitation have mostly come from retrospective reports of rhabdomyolysis in subjects with crush injuries. Inadequate volume repletion can result in AKI, and therapy instituted much later can increase the incidence of AKI in over 50% of patients (35).

Crush syndrome-related AKI can be prevented by enhancing kidney perfusion and increasing urine flow to wash out obstructing casts. The goal of preventive therapy is to correct volume depletion as soon as possible. Fluid administration should be started before extrication in entrapped subjects who are prone to develop Crush syndrome. The volume of fluids should be adjusted at a rate of 1 L per hour. Patients with rhabdomyolysis may require massive amounts of fluid (up to 20 liters) to trigger and maintain a vigorous diuresis. Children similarly require early and aggressive fluid resuscitation (36). Fluid administration should be closely monitored, with the timing and rate of fluid administration, volume of fluids, and

types of fluid all considered. Intravenous fluids at the rate of 15 to 20 mL/kg/h should be started when the victim is still under the rubble. If extrication takes longer than two hours, then the rate of fluid administration should be reduced to 10 mL/kg/h or lower (36). If fluids cannot be given before extrication, then volume resuscitation should begin as soon as possible after extrication.

It is important to note that the optimal type and rate of fluid repletion may vary depending on the individual patient's medical condition and response to treatment.

Generally, the recommended fluid administration rate for the first 24 hours is 500 mL/hour, provided there is no evidence of fluid overload, and the patient can be closely monitored. The rate of fluid administration is reduced after the first 24 hours but is still maintained at a rate higher than the urine output if there is no evidence of fluid overload. The amount of fluid administered to a patient is influenced by various factors such as age, weight, medical history, and the specific clinical scenario. The appropriate fluid balance is crucial in the early stages of treatment. In the early phase of Crush syndrome, excessive fluid can seep into the damaged muscles, making fluid administration critical. For an adult weighing 75 kg and with an appropriate urine response, up to 12 L of fluid can be administered per day. After the infusion of this solution, one can expect a urinary output of 8 liters. Therefore, it is reasonable to give 4 to 4.5 L more fluid than the total losses of the previous 24-hour period (19). In chaotic disaster situations where monitoring patients is difficult, fluid administration should be less aggressive to avoid volume overload (37). In these circumstances, it is recommended to give a more modest volume of fluids, up to a maximum of 6 L per day when close monitoring is not possible. In older adults or anuric patients, who are prone to cardiac failure, it is particularly important to be cautious when repleting fluids.

However, in the absence of direct comparative studies, the Renal Disaster Relief Task Force (RDRTF) of the International Society of Nephrology (ISN) recommends the use of isotonic saline as the preferred fluid for volume replacement during extrication in the context of a massive disaster (38). This recommendation is based on the availability and well-described efficacy of isotonic saline for this purpose.

If isotonic saline plus 5% Dextrose is available, it may be used as an alternative since it provides the added benefit of supplying calories and attenuating hyperkalemia. However, the use of bicarbonate added to hypotonic saline as a replacement fluid is not recommended due to the lack of evidence supporting its efficacy in this setting and the potential for adverse effects (38).

In cases of metabolic acidosis, bicarbonate therapy is used to alkalinize the plasma. It should be used with caution due to its potential risks, such as promoting calcium phosphate deposition and inducing or worsening the manifestations of hypocalcemia by both a direct membrane effect and a reduction in ionized calcium levels. The target urine pH is >6.5, and bicarbonate administration is discontinued if the arterial pH exceeds 7.5, the serum bicarbonate exceeds 30 mEq/L, or the patient develops symptomatic hypocalcemia (39).

The use of mannitol in preventing AKI is a topic of controversy, as its effectiveness is uncertain and may even be harmful in patients with rhabdomyolysis (40). It is important to note that mannitol should not be administered to patients with oligoanuria. Before administering mannitol, it is important to perform a test dose to determine if there is an increase in urine output (41). If a desired diuresis of around 200-300 mL/hour is not achieved, mannitol administration should be stopped to avoid the risk of hyperosmolality and volume overload.

To prevent hyperkalemia, oral administration of gastrointestinal cation exchangers like sodium zirconium cyclosilicate (SZC) or patiromer can be given. SZC is the preferred option due to its faster onset of action, although its efficacy has not been tested in disaster victims. In situations where SZC and patiromer are not available or unaffordable, sodium polystyrene sulfonate (SPS) can be administered (10).

Isotonic solutions used for fluid repletion often contain potassium, which can cause hyperkalemia in patients with Crush syndrome. Therefore, the use of such preparations is contraindicated in these patients. Plasma potassium levels should be monitored frequently until stabilized (41).

In case serum potassium concentration cannot be measured due to field conditions, electrocardiography (ECG) can provide useful information. In disaster situations, point-of-care devices like iSTAT can be used to measure electrolyte and creatinine levels directly and detect hyperkalemia early, identifying patients who require urgent dialysis (42).

A retrospective analysis of a large series after acute trauma has shown that nephrotoxic drugs play an important role in the development of AKI in at least one-third of patients (43). Another analysis conducted on the treatment of the Marmara earthquake showed that a considerable quantity of nephrotoxic antibiotics and NSAIDs were administered. Hence, it is imperative to meticulously review all the drugs administered to patients during each visit and discontinue the use of any nephrotoxic drugs.

For patients who have not had a bladder catheter inserted before hospitalization, one should be placed after excluding urethral bleeding or laceration that is characterized by blood at the urethral meatus. However, the use of catheters carries a risk of infection, especially during disasters (41). Therefore, catheters should only be used

when necessary, such as in cases of unconsciousness, pelvic trauma, possible urethral obstruction, immobilization, or surgery. The catheter should be removed, unless there is an obligatory indication.

The management of Crush syndrome requires careful attention to maintaining renal perfusion and avoiding fluid overload. One crucial aspect of this management is the urine output goal, which is set at approximately 200 to 300 mL/hour for patients who can be closely monitored, such as in a hospital or triage setting. However, it is essential to monitor patients closely to prevent fluid overload, which can lead to pulmonary congestion. Limb swelling alone may not represent volume overload, and other signs should be taken into account. Although frequently used to determine volume status, absolute CVP values can be misleading and often do not predict the response to volume infusion. Absolute values are increased not only in hypervolemia, but also in other disease states, such as cardiac failure. For that reason, relative changes may be more useful than absolute values in reflecting intravascular volume status (44).

Treatment

Conservative treatment for AKI includes measures such as adequate hydration, discontinuation of nephrotoxic medications, and treatment of underlying medical conditions. In addition to conservative treatment, dialysis may be initiated and used as intensively as necessary to manage the patient's condition.

Consequently, the therapeutic approach during the oliguric period differs significantly from that during the subsequent polyuric phase. The duration of oliguria can vary widely, depending on the length and severity of the initial ischemia, the recurrence of ischemia, and the association of nephrotoxic insults. Some patients may recover within days, while others may require dialysis for a week (41).

Given that most of the life-threatening complications occur during the oliguric period, it is essential to closely monitor patients during the first 2 weeks of treatment. Once patients survive this period, most will eventually recover kidney function and be discharged.

AKI can be treated with various renal replacement therapy options, including intermittent hemodialysis, continuous renal replacement therapy, and peritoneal dialysis. Each modality presents unique medical and logistical challenges (45), (Table 1).

Table 1: Unique advantages and disadvantages of different renal replacement therapy modalities

RRT Type	Advantage	Disadvantage
IHD	- High clearance rate of low molecular weight solutes - Possibility of anticoagulant-free dialysis - Possibility to dialyze more than one patient on a single machine on the same day	- Technical equipment and experienced personnel are required - Set priming may aggravate the picture in hypotensive or hypotension-prone patients - Higher risk of dialysis imbalance syndrome
CRRR	- It provides better fluid control - Reduced risk of dialysis imbalance syndrome - Possibility of higher calorific intake - CAVH provides the advantage of treatment without the use of electricity and pumps - Equipment requirement is very low	- Requirement for continuous heparinisation in patients with hemorrhage or hemorrhagic diathesis - Low removal capacity for small molecular weight solutes - Capacity to treat only one disease per machine - The need to transport heavy and bulky fluid bags to the disaster site
PD	- Possibility of dialysis without the need for vascular access - Simpler technique and fewer hemodynamic problems - No requirement for water or electricity infrastructure	- Low clearance for low molecular weight substances - Dialysis may be difficult under sterile conditions - May be contraindicated if the patient cannot lie supine or has abdominal wall infection, intestinal obstruction, large abdominal hernia, marked obesity and/or aortic aneurysm - The need to transport heavy and large fluid bags to the disaster area

RRT: Renal Replacement Therapy, IHD: Intermittent haemodialysis, CRRT: Continuous renal replacement therapies, PD: Peritoneal dialysis, CAVH: Continuous arterio-venous haemofiltration

Intermittent hemodialysis is an effective option that can treat multiple patients with a single dialysis machine in a day. Short sessions of two to three hours can prevent life-threatening hyperkalemia. But this approach requires technical support, experienced personnel, electricity, and water supplies, which may be difficult to access during a disaster.

Continuous renal replacement therapy is another option that can gradually remove solutes and fluid. However, it can only treat one patient per machine and requires experienced personnel, electricity, and large quantities of substitution fluid. Moreover, continuous anticoagulation can cause bleeding in patients who are severely injured.

Peritoneal dialysis is a technically simple option that can be initiated quickly, and it requires no electricity or tap water supplies. However, it may be challenging to use in patients with abdominal or thoracic trauma, and it requires substantial quantities of sterilized dialysate. In non-hygienic field conditions, it can result in complications. Moreover, both continuous renal replacement therapy and peritoneal dialysis are less efficient than intermittent hemodialysis in removing potassium.

In light of all this information, although CRRT or PD can be used depending on availability and patient needs, IHD should be preferred as the first choice in renal replacement therapy. Conventional dialysis indications are also valid in this patient group. However, it may be more liberal to start dialysis in patients with crush-related AKI due to the frequency of fatal complications such as severe hyperkalemia (41).

Logistic issues

Disasters occur intermittently; therefore malpractice is frequent during disasters (46). Also, there is a disparity between healthcare demand and supply, which results in not only logistic but also ethical dilemmas (47). Both of these drawbacks can be minimized by predisaster preparedness, which targets improving problems towards disaster-related medical information and interventions and also reducing post-disaster chaos (48). These preparations may take place at international, national, and regional levels, and aim to answer the questions of who, when, what, and how before, during, and after disasters (49). Discussing all these issues is out of the scope of this review, and the reader is referred to other sources for a detailed description of these problems and their solutions (49, 50).

CONCLUSIONS

Crush syndrome is the second most frequent cause of deaths following the direct impact of trauma in destructive disasters. Although its clinical course is highly complicated, which necessitates intact city and medical infrastructure, and also experienced personnel, surviving patients may enjoy full recovery and rehabilitation as well. Therefore, careful follow-up and proper treatment of these patients are vital in order to save as many lives as possible after mass disasters.

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CHILD HEALTH PROTECTION DURING EMERGENCY SITUATIONS

OLAĞANÜSTÜ DURUMLARDA ÇOCUK SAĞLIĞININ KORUNMASI

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ABSTRACT

Natural disasters such as earthquakes are emergency situations when the fragility of the entire society, especially children, increases. In emergency situations, breastfeeding is crucial due to its unique characteristics: nutrient and bio-immunological content, optimum temperature and readiness for the baby. Ensuring healthy nutrition, maintaining childhood vaccination, preventing infectious diseases, providing sheltering and child safety, and preserving mental health are the basic issues in protecting child health during emergencies. Following the children who have experienced a disaster currently is necessary regarding long-term physical and psychological effects. Moreover, monitoring the growth and development, maintaining the care of children with chronic diseases, and continuity of school attendance are essential under these circumstances. The aim of this article is to present the basic principles of child health protection during emergency situations.

Keywords: Child health, disasters, emergency situations, breastfeeding, wet nursing, vaccination

ÖZET

Deprem gibi doğal afetler, başta çocuklar olmak üzere tüm toplumun kırılganlığının arttığı acil durumlardır. Acil durumlarda, besleyici özelliği, biyoimmünolojik içeriği, ideal sıcaklıkta ve hazır olması nedeniyle benzersiz özelliklere sahip anne sütü ile beslenme çok önemlidir. Sağlıklı beslenmenin sağlanması, çocukluk çağı aşılarının uygulanması, bulaşıcı hastalıkların önlenmesi, barınma ve çocuk güvenliğinin sağlanması, ruh sağlığının korunması acil durumlarda çocuk sağlığının korunmasında temel konulardır. Afet yaşayan çocukların takibi, uzun süreli fiziksel ve psikolojik etkiler açısından gereklidir. Ayrıca büyüme ve gelişmenin izlenmesi, kronik hastalığı olan çocukların bakımının sürdürülmesi ve okula devamın sağlanması gereklidir. Bu makalenin amacı, acil durumlarda çocuk sağlığını korumanın temel ilkelerini sunmaktır.

Anahtar Kelimeler: Çocuk sağlığı, afetler, acil durumlar, emzirme, süt annelik, aşı uygulamaları

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GENİŞ ÖZET

Makalede olağanüstü durumlarda çocuk sağlığının korunması için gereken prensiplerin bilimsel veriler ışığında sunulması amaçlanmıştır.

Her koşulda bebeklerin ve küçük çocukların sağlıklarının korunması için ilk 6 ay tek başına anne sütü ile beslenmelerinin sağlanması ve anne sütü ile beslenmenin en az 2 yaşına kadar sürdürülmesi önerilmektedir. Anne sütü hayati önem taşır çünkü güvenlidir, besleyicidir, ideal sıcaklıktadır ve hazırlanması gerekmez. Besleyici özelliklerinin yanı sıra içerdiği antikorlar, lizozim, laktoferrin, oligosakkaritler, büyüme faktörleri gibi biyoaktif bileşenleri ile anne sütü bebeği birçok bulaşıcı hastalıktan korur ve ileri yaştaki kronik hastalık riskini azaltır. Afetlerde annelerin yaşadıkları stres nedeniyle annelerde süt inme refleksi baskılanabilmekte, geçici olarak süt yapımı azalabilmektedir. Bu durum doğru yaklaşım ile üç günde düzelmektedir. Annelerin bebeklerini sık emzirmeye ve uzun süre memede tutmaya devam etmeleri süt yapımını yeniden artırmaktadır. Her anne kendi beslenme durumundan bağımsız olarak bebeğini başarı ile emzirebilir. Emziren annelerin mümkün olduğunca emzirmeyi sürdürmeleri ve bebeklerin anne sütü almaları olağanüstü durumlarda daha da önemlidir. Bunun için anneler korunmalı ve desteklenmelidirler. Özellikle altı aydan küçüklerin anne sütü alamadıkları durumlarda sağlık çalışanlarının kontrolünde süt veren başka bir annenin sütanne olması sağlanabilir. Bu durumda anne sütü doğrudan memeden ya da hijyen koşullarına dikkat edilerek elle sağılıp fincanla verilebilir.

Dünya Sağlık Örgütü, UNICEF ve ülkelerin sağlık bakanlıkları olağanüstü koşullarda emzirmeye devam etmenin çok önemli olduğunu vurgulamakta, doğrudan halka mama dağıtımını önermemektedir. Anneden ayrı olması gibi bebeğin annesinin sütünü alamadığı özel koşullarda ve süt annenin bulunmadığı durumlarda formül mama gerekebilir. Kamu sağlık görevlilerinin kontrolü dışında hazır mama dağıtımı, anne sütünden yararlanmayı olumsuz etkilemekte bebeklerin büyüme ve gelişmesinde kısa ve uzun dönemde önemli sorunların yaşanmasına neden olmaktadır. Olağanüstü durumlarda formül mama ile beslenen bebekler için en güvenli tercih, suyla karıştırılması gerekmeyen sıvı bebek mamalarıdır. Tek seçenek toz formül mama ise; ölçü kaşığı kullanılarak mama hazırlanmalı, sulandırılması sırasında su sıcaklığı 70°C ve üzerinde olmalıdır. Mamanın soğutulması sulandırıldıktan sonra yapılmalıdır. Temizlik açısından hazırlanan mama biberon yerine fincan ile verilmelidir. Anne sütü olmayan ve mama ile beslenen 4 aydan büyük bebeklere meyve püresi, yoğurt ve sebze püresi uygun şekilde hazırlanarak verilebilir. Büyük çocuklarda kolay hazırlanan besinler tercih edilmelidir. Bölgede yetişen meyve ve sebzenin kullanımı sağlıklı beslenmenin sürdürülebilirliği açısından önemlidir.

Afetlerde ishaller ve solunum yolu enfeksiyonları en sık görülen çocuk ölüm nedenleri arasında yer alır. Anne sütü ile beslenen bebeklerde bu hastalıklar daha az görülür ya da görülse de daha hafif seyreder. Anne sütü yerine kullanılan ürünler özellikle toz mamalar kontamine su, kötü hijyen ve besleme aletlerinin uygun olmayan şekilde temizlenmesi enfeksiyon riskinin artmasına neden olur. Anne sütü almayan bir bebeğin patojenlerle enfekte olma, yetersiz beslenme ve ölüme yol açan çok sayıda ağır hastalığa yakalanma olasılığı daha yüksektir. Deprem sonrası yapılmış bir çalışmada; bağışlanan bebek maması alanlarda ishal insidansının almayanlara göre daha yüksek olduğu belirlenmiştir. Mamaların kontrolsüz dağıtımı, bebeklerde ve küçük çocuklarda ishal riskini artırmaktadır.

Afetlerde aşı uygulamaları aksayabilmektedir. Çocukların aşılanma durumları değerlendirilmelidir. Önceki aşı kayıtlarına ulaşılabiliyorsa yaşa uygun aşılamaya devam edilmeli, kayıtlarına ulaşılamıyorsa hiç aşısız kabul edilerek program oluşturulmalıdır. Kesintiye uğramış programlarda aşılama kalınan yerden sürdürülür. Fekal oral bulaş riskinin arttığı olağanüstü durumlarda hepatit A ve polio aşılamasının aksamaması çok önemlidir. Sağlık hizmetlerine erişimde güçlük, yerleşim kamplarındaki aşırı kalabalık ve hızlı nüfus hareketleri kızamık gibi bulaşıcı hastalıkların riskini artırır. Kızamık Eliminasyon Programı'nda belirtildiği gibi riskli bölgelerdeki; 6 ay üzeri çocukların kızamık aşılanma durumlarının değerlendirilmesi gerekmektedir. Depremde yaralananlar tetanos profilaksisi açısından değerlendirilmelidirler. Kafa travması olanlar olası beyin omurilik sıvısı kaçağı nedeniyle konjuge pnömokok aşısı ile yaşına uygun eksiksiz aşılanmalı, iki yaşından büyüklere, konjuge pnömokok aşısından en erken 8 hafta sonra polisakkarit pnömokok aşısı da yapılmalıdır. H. İnfluenza Tip b, Meningokok ACWY ve B aşıları da çocuğun yaşına ve aşılanma durumuna göre uygulanabilir. Afetlerde deri enfeksiyonlarından korunmak için çocukların saç, tırnak ve deri temizliğinin düzenli olarak yapılması; hava koşullarına uygun temiz kıyafetlerin ve ayakkabıların giyilmesi önemlidir.

Depremlerde güvenli barınma alanlarının sağlanması önceliklidir. Çocuklu aileler, kimsesiz ya da refakatçisiz çocuklar en kısa sürede güvenli alanlara nakledilmelidirler. Bölgelerde çocuklara kol bandı takılmalıdır. Doğal afetlerde çocuk istismarı riski artmaktadır. Bu nedenle, bölgedeki çocuklara uygun sosyal desteğin ve okul devamlılığının sağlanması çok önemlidir. Çocuk güvenliğinde kamu görevlileri yer almalı, refakatçisiz çocukların korunması devlet tarafından organize edilmelidir.

Afetlerde çocukların sevgi ve ilgiye ihtiyaçları artar. Anne sütü ile beslenmenin sürdürülmesi; emzirme sırasında salınan hormonların etkisi ile hem anne hem bebeğin ruhsal sağlığı için önemlidir. Oyunla meşgul etmenin yanı sıra beş yaşından büyüklere görev vermek; endişelerini hafifletir, onları oyalar. Spor aktiviteleri, çocukların stresle baş etmelerine yardımcı olur. Çocukların günlük düzenlerinin olması kendilerini güven içinde hissetmelerini sağlar. Yetişkinlerin fiziksel ve ruhsal sağlıklarının iyi olması, bakım verdikleri çocukları da olumlu etkiler. Çocukların yetişkinleri üzgün veya ağlarken görmelerinde sakınca yoktur; ancak çığlık atmak, etrafa vurmak gibi davranışlar korkutucu olabilir. Çocuklara anlaşıldıkları ve güvende oldukları hissettirilmelidir. Afet sonrası çocuklarda olayı yeniden yaşama ve yüksek kaygı görülebilir. Bulguların bir aydan uzun sürmesi travma sonrası stres bozukluğunu düşündürmeli ve sağaltımı için uzmanlar ile iş birliği yapılmalıdır.

Sonuçta olağanüstü koşullarda çocuklar en hassas grubu oluştururlar. Bu nedenle afetlerde çocuk sağlığına yönelik tedbirler iyi bilinmeli ve süratle hayata geçirilmelidir.

INTRODUCTION

In natural disasters, the fragility of the entire society increases, but children and the elderly constitute the most vulnerable group. The mortality rates in children increase during emergency conditions (1-3). Acute respiratory infection, diarrhea, malnutrition and communicable diseases like measles are the leading causes of child deaths in disasters (4).

Healthy nutrition and breastfeeding, prevention of infectious diseases and vaccination, sheltering and mental health are the basic issues for protecting children's health during emergency situations. The aim of this article is to explain these issues in detail in the light of current scientific studies.

Ensuring healthy nutrition, maintaining breastfeeding

In all circumstances, the World Health Organization (WHO), UNICEF and health ministries of the countries recommend to start breastfeeding immediately after birth, continue exclusive breastfeeding for the first 6 months, and carry on breastfeeding for up to 2 years and beyond to protect the health of infants and young children (5,6).

Breast milk is crucial because it is safe, nutritious, at an optimum temperature, accessible, ready to use and provides protection against infections. Breast milk is a living substance and has a dynamic structure. In addition to its nutritional properties, soluble components such as secretory antibodies, lysozyme, lactoferrin, oligosaccharides, and growth factors; cellular components such as neutrophils, macrophages, epithelial cells; and microbiota components such as Bifidobacterium, constitute bioactive components in breast milk. With its both nutritional and bioactive content, ideal nutrition is provided, infectious diseases are prevented, and the risk of chronic diseases is reduced. Most of these effects continue throughout life. In each feeding period, there may be changes in the components of breastmilk according to the biological, social, and psychological needs of the mother and baby. For example, it is now well known that antibodies increase in the mother's milk during a mother's or infant's infectious disease (7,8). Underinvestment in the protection, promotion and support of breastfeeding will lead to the lack of benefits of breastfeeding and an estimated US$341.3 billion lost worldwide each year (9). Successful breastfeeding is a common responsibility of not only the mother but also the social environment.

According to Turkish official statements, more than 2500 babies were born during the first week after the earthquake in the region in 2023 (10). In emergency situations, newly delivered mothers must be supported to start breastfeeding immediately after birth and all breastfeeding mothers should continue breastfeeding. Milk production may decrease temporarily in emergencies due to the letdown reflex suppression with the effect of stress and shock, as seen in some mothers during the 1999 earthquake in the Marmara region. This suppression improves with the right approach in three days. If mothers continue to breastfeed their babies at least 8 times in 24 hours, during night as well, and keep the baby at the breast, milk production will increase again (11). Hormones such as oxytocin and prolactin secreted during breastfeeding also reduce stress in mothers and babies (12). Therefore, breastfeeding counseling becomes even more important in emergency situations (1,4,9,12-15). The algorithm for maintaining breastfeeding in the first six months of life in emergency situations is summarized in Figure 1. Hand expression of the breastmilk (Figure 2) and cup feeding (Figure 3) may be needed under these circumstances.

If the mother needs to use medication due to a health problem, the compatibility of drugs used with breastfeeding should be checked without interrupting breastfeeding, and the drug can be changed in case of doubt. Situations where breastfeeding is not recommended because of an infectious disease or the mother's medications are very rare (Figure 1, c section). LACTMED, an up-to-date database on drug use during breastfeeding, can be used (16).

When the biological mother is not available, another mother can breastfeed under the control of health workers (4). However, it should be ensured that the baby and nursing mother to-be have no contraindications for breastfeeding (17-19). Health professionals should make a detailed assessment of these criteria (13).

The health ministries of all countries in the world, with the leadership of WHO and UNICEF, emphasize that it is crucial to continue breastfeeding under emergency conditions and do not recommend distributing formula directly to the public (4-6,15). In exceptional circumstances, such as the loss of the mother, formula milk can be given if there is no other available breastfeeding mother (Figure 1) (4-6, 20). The distribution of the formula should be under the strict control of the public health personnel. The situations in which formula milk should be given are very limited and should be determined by public health officials. The safest choice for formula-fed infants in emergencies is ready-to-use infant formulas that do not require water (13,20). However, if the only option is a powdered formula, attention should be paid to preparing it under sterile conditions. Accessing safe water for cleaning feeding bottles and teats could be a problem. If a reliable water source is unavailable, the equipment must be boiled in water for 20 minutes before each feeding. However, the prepared food should be given in a cup to minimize contamination (Figure 3) (4,14,21). Once opened, infant formula containers must be stored in a cool, dry place with a tightly closed lid (20).

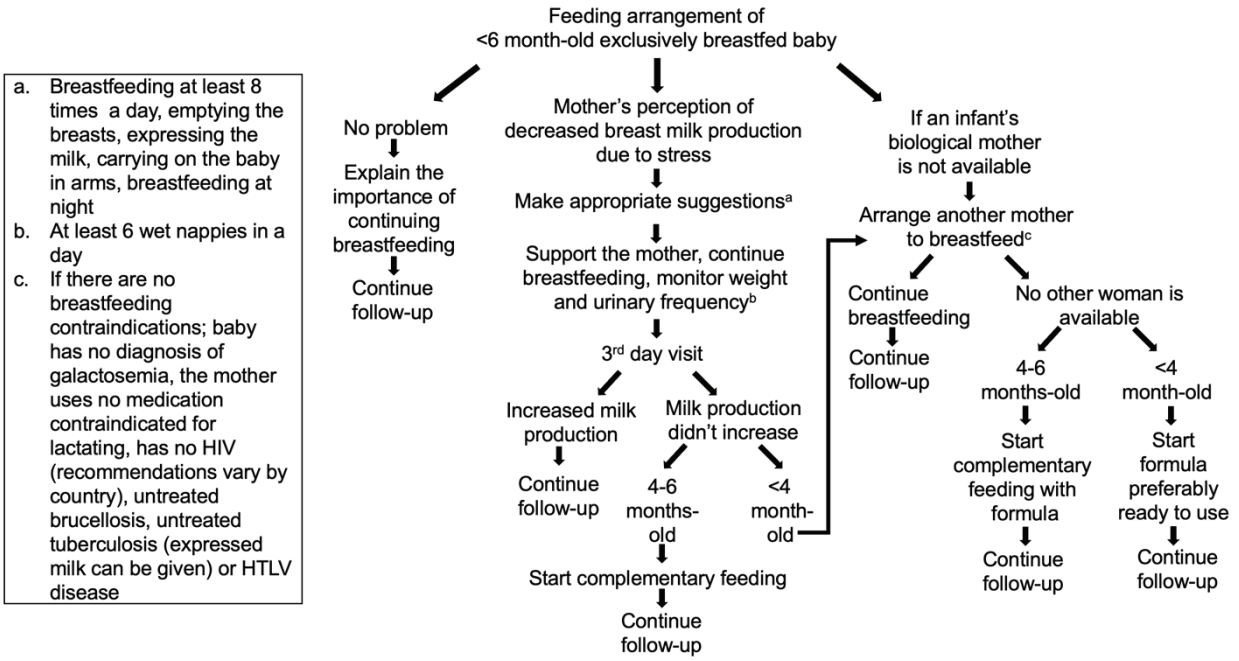
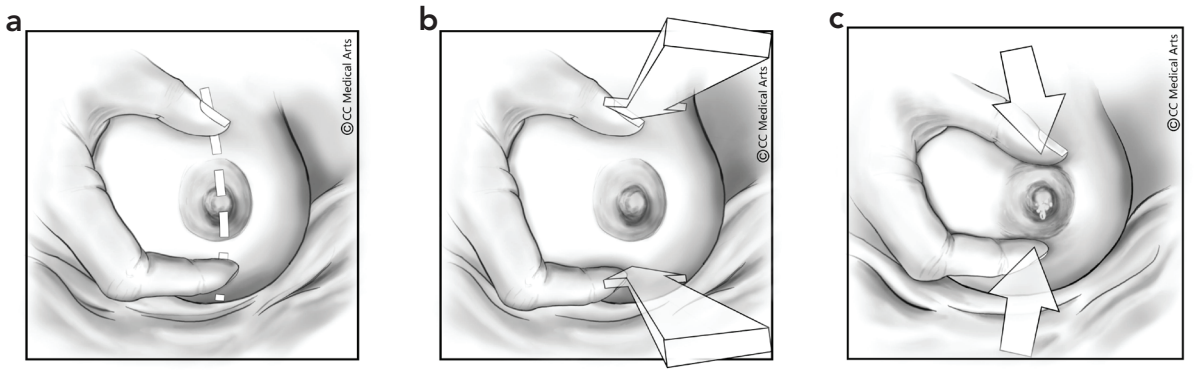


Figure 1: Breastfeeding in the first six months of life in emergency situations (4,16,17,19).



- The index finger under the brown part of the breast, the thumb on the breast, above the edge of the brown area. The nipple on the same line between the thumb and index finger (a).
- Thumb and index fingers are pressed against the chest wall to feel the underlying tissue (b).
- The fingers are brought closer together to tighten the breast tissue, and then the fingers are released (c).
- This movement should be repeated regularly, and the mother should adjust the speed, pressure, and rhythm according to her own needs.

Figure 2: Expressing milk by hand

The persons who will provide formula feeding should be informed about the safe preparation of formula (4,). A safe water source will be bottled water (22). Formula milk should be prepared with boiled water and a sterilized measuring spoon. It is important that the water temperature is 70°C and above until the powder is dissolved, and cooled after dissolution (23). If any made-up formula is left in the bottle after a feed, it must be discarded. Properly prepared fruit, yoghurt, and vegetable puree can be given to infants 4 months and older who do not receive breast milk and are fed with formula (14,24).

For older children, foods that are easy to prepare can be consumed. Fruits and vegetables grown in the region are essential for a healthy diet's sustainability. Regulation of easily accessible foods such as eggs and milk to ensure protein intake is necessary for healthy nutrition in collective living conditions after disasters.

Figure 3: Cup feeding technique (21)

Infectious diseases such as diarrhea and respiratory infections are less common in breastfed babies, and when rarely seen, the course tends to be milder. Breast milk substitutes, especially powdered formula, may also act as a vector of infection due to contaminated water, poor hygiene and improper cleaning of feeding utensils. A non-breastfed infant is more likely to be infected with pathogens, malnutrition, and many serious illnesses that lead to death (1,25). On the other hand, introducing a bottle of formula to a breastfed baby may adversely affect the infant's breastfeeding irreversibly. A study conducted after the earthquake, which took place in Indonesia in May 2006, reported that infant formula consumption of children aged 0-5 months was 32% before the earthquake, and this rate increased to 75% with the donated formula after the earthquake; consequently, the rate of breastfeeding decreased. It was found that the incidence of one-week diarrhea was higher in those who received donated formula than in those who did not, and the rate of diarrhea in children aged 12-23 months increased five times compared to the pre-earthquake time period. The research results showed that the uncontrolled formula distribution increased the risk of diarrhea among infants and young children in emergency situations such as earthquakes (26).

Prevention of infections and vaccination

In the disaster areas, difficulty in accessing clean water, infrastructure damage, crowded temporary living environments, and excessive population movement pose risks of some epidemic situations such as diarrhea, pneumonia, and scabies (4, 27).

Hand cleaning with soap and water for 15 seconds becomes even more important under emergency situations. However, cleaning wipes can be used if there is no access to soap and water. Cleaning and brushing hair, nails, and skin regularly becomes even more critical in emergency situations (14,28). Disposable baby diapers are needed to prevent skin infections and should be changed immediately if dirty, and every 3 hours, even if not dirty. Leaving the diaper area open for 20 minutes every day helps to prevent diaper rash. If a diaper rash appears, starting the treatment immediately is necessary to prevent severe skin infections.

In emergency situations, where infectious diseases increase due to poor environmental conditions, there may be disruptions in immunizations (29,30). Vaccination of children should be evaluated. If the previous vaccination records can be accessed, age-appropriate immunization should be checked. If their records cannot be reached, they should be considered unvaccinated, and a vaccination program should be established. In this regard, the Ministry of Health guidelines and the vaccination recommendations for the unvaccinated child on the Social Pediatrics Association website can be used (31). The interrupted or delayed vaccination program should be resumed from where it had been left off (32).

Considering that the risk of fecal-oral transmission may be increased in disasters, hepatitis A and polio vaccination should not be missed. Difficulty accessing health systems, overcrowding in camps, and rapid population movements significantly increase the risk of measles infection (33). As pointed out in the Measles Elimination Program of the Ministry of Health of Türkiye, risky areas should be determined. In these risky areas, everyone aged above six months should be evaluated to be vaccinated against measles (34).

Children injured during an earthquake must be evaluated for tetanus prophylaxis (35) (Table 1). Children with head trauma and possible cerebrospinal fluid leakage must receive a pneumococcal conjugate vaccine (PCV13) as per the standard schedule. If these children are older than 2 years of age, they should also receive the pneumococcal polysaccharide vaccine at least 8 weeks after the last PCV13 (36,37). Administration of one dose of H. Influenza Type B vaccine is also recommended after 60 months of age, even if fully vaccinated. Meningococcal vaccination can be considered for these children as well (36-38).

After disasters, the population in the camps is the most socioeconomically disadvantaged group and may be more likely to be under-vaccinated (2). Furthermore, con-

Table 1: Tetanus vaccine and immunoglobulin recommendations for injuries (35)

Vaccination history (dose)	Clear small wounds		All other wounds [a]	
	Vaccine [b]	TIG [c]	Vaccine [b]	TIG [c]
Unknown or <3 dose	Yes	No	Yes	Yes
3 or more doses	No 'Yes' (if >10 years have passed since the last dose)	No	No 'Yes' (if >5 years have passed since the last dose)	No

a: Other wounds; wounds contaminated with feces, soil, saliva, penetrating wounds, crushing wounds, burn and frostbite wounds and other dirty wounds, b: Vaccine administration can be done as DTaP, Tdap or Td, c: TIG: Tetanus immunoglobulin; TIG dose is 250 IU for all ages.

sidering the excessive population movement after the earthquake, necessary arrangements should be made to continue immunization.

Sheltering and child safety

Providing safe shelters after disasters is a priority for child health (30). The first step in preventing an unsafe environment for children after a disaster is ensuring to receive humanitarian support (39). Families with children and unaccompanied or orphaned children should be transferred to safe areas as soon as possible. Persons and all children living in the disaster areas should be listed. Armbands must be provided to all children. Public officials play a crucial role in child safety. They organize the government protection of unaccompanied children (14,30).

Studies show that child abuse increases during emergency situations (30, 39,40). In the circumstances such as the loss of a parent during natural disasters or living in camp areas, children are faced with risks such as accident, disappearance, kidnapping, and early marriage. Therefore, it is vital to provide appropriate social support to children at risk, maintain school attendance, and ensure that care and support services are provided to children in emergency situations.

Mental health and communication with the child

After disasters, children may experience anxiety, fear, sadness, sleep disturbances, difficulty in concentration, irritability, and outbursts of anger. Stress and mental problems affect children's physical health, quality of life, and behavior at home, school, and other social settings (41). Children's need for love and attention increases in disasters. Breastfeeding and hugging are effective in calming babies (42). It is helpful to keep children busy with various games. Ensuring children's sleeping and feeding times are in daily order will make children feel safe. Adults' good physical and mental health also positively affects the children. There will be no problem if children and teenagers see adults sad or crying, but overreactions such as screaming, banging or kicking can be frightening for children (43).

Play and sports activities are among the best ways for children to cope with stress. Instead of watching television, engaging in interactive play activities makes it easier to overcome post-traumatic stress reactions. Establishing pre-fabric schools in the area as soon as possible is very important in this respect (30). Children are allowed to express their fear, anxiety or anger. This "non-permanent" situation should be kindly explained.

Children directly exposed to a disaster may become sad when they see or hear things that remind them of the unfavorable past events. Exposure to mass media related to the disaster can make them uneasy. In addition, responsibility can be given to children to support others in the disaster area to regain their sense of control and help them to manage their emotions. However, participating in post-earthquake cleaning activities in the debris field is not appropriate for small children (41,44-46).

The communication principles during the first encounter are listed in Table 2 (42). After traumatic events, post-traumatic stress reaction, anxiety, and depression-like symptoms may occur in children. During emergency situations, post-traumatic stress reaction should be considered in the presence of the main findings, which are re-experiencing the trauma, avoidance of the trauma reminders, increased anxiety and overstimulation (47). Observation of these findings in the first month is defined as an acute stress reaction, and if it lasts longer than one month, considered as post-traumatic stress disorder (PTSD). If PTSD is present, cooperation with child and adolescent psychiatry and mental health specialists is required. PTSD in children after disasters is reported to be between 5% and 58% (47). PTSD symptoms may continue in children for two or three years (48). Depression and anxiety may accompany PTSD in children and adolescents (47,48). Suicidal thoughts were also reported to be common among adolescents after the disaster (49).

The frequency of internalization (finger sucking, depression, etc.) and externalization (hyperactivity) type behavior problems increases in the children of parents with PTSD. Therefore, supporting the mental health of

Table 2: Communication principles with children in the disaster area during the first intervention period (41)

- Calm, compassionate and ready to listen approach
- Introducing yourself by name and explaining the reasons to be there.
- Short and clear talk; maintaining eye contact at the same level is important while speaking.
- Informing the child that he is safe, and calling him by name if known.
- Providing information about what has been done. For example, it should be said that "we are going to a hospital by ambulance to check your health".
- Being sensitive to the need of the child.
- Avoiding being overly anxious, sad, affectionate or angry in the presence of the child
- Limited use of communication tools (TV, social media) for the news about disaster next to the child.
- Keeping children away from media exposure for privacy and respectability.
- Encouraging children to speak spontaneously, not forcing
- Obtaining children's consent while helping them.
- Avoiding to give information about death or loss during the first contact.
- Making explanations about the loss, in the presence of psychologists or social workers.
- Taking information (name, surname, telephone number etc.) about the child's parents and relatives, recording and reporting to the relevant units.

parents is also important in terms of the child's mental health (50). Furthermore, continuing breastfeeding has a protective effect in the short and long term on the mental health of both mother and baby, with the impact of hormones released during breastfeeding (12).

CONCLUSION

Ensuring healthy nutrition, preventing infectious diseases and maintaining childhood vaccination, providing sheltering and child safety, and preserving mental health are the basic issues in protecting child health during emergencies. All children who have experienced a disaster need to be closely followed up regarding the long-term physical and psychological effects of the disaster. Preservation of breastfeeding, close monitoring of growth and development, and maintenance of school attendance are crucial for child health protection.

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A CASE REPORT OF A RARE NONSENSE *ZP1* VARIANT IN A PATIENT WITH OOCYTE MATURATION DEFECT*

OOSİT MATÜRASYON DEFEKTİ OLAN BİR OLGUDA NADİR GÖRÜLEN ANLAMSIZ *ZP1* VARYANTI

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ABSTRACT

After four unsuccessful assisted reproductive techniques trials, a female was referred for genetic analysis. In this case study, we aimed to investigate the genetic etiology of a female with infertility and oocyte maturation defect. Chromosome analysis and fluorescence in-situ hybridization (FISH) using X-centromeric (DXZ1) and SHOX-probe (SHOX/SE X) (CytoCell, Cambridge, UK) on interphase nuclei of lymphocytes and mucosal cells were performed. Exome sequencing using the Illumina platform and confirmatory studies, including intra-familial segregation analysis, was done by Sanger sequencing. Karyotyping and molecular cytogenetics studies were normal, and potential chromosomal abnormalities and mosaicism were excluded. WES data analysis identified a known, rare, nonsense pathogenic homozygous variant in exon 3 (NM_207341.4, c.628C>T; p.Q210*) of the *ZP1* gene. Additionally, her parents, who were first-degree cousins, were heterozygotes for this variant. Zona pellucida is an essential glycoprotein that surrounds oocytes and contains four types of receptor proteins (ZP1-4). The detected mutation in the *ZP1* gene leads to the premature stop codon, causing truncation of the ZP1 receptor protein. This is the first case report with a homozygous variant associated with oocyte maturation defect. Also, exome sequencing is a valuable method to identify the genetic etiology in complex, multigenic conditions like infertility.

Keywords: OOMD, zona pellucida, *ZP1*, female infertility, exome sequencing

ÖZET

Bu çalışmada yardımcı üreme tedavisi sonrasında dört başarısız denemesi olan kadın bir olguda, infertilite ve oosit olgunlaşma bozukluğunun genetik etiyolojisinin araştırılması amaçlanmıştır. Lenfositlerin ve mukozal hücrelerin interfaz çekirdekleri üzerinde X-sentromerik (DXZ1) ve SHOX-probu (SHOX/SE X) (CytoCell, Cambridge, UK) kullanılarak kromozom analizi ve floresans hibridizasyonu (FISH) yapıldı. Ekzom dizilemede Illumina platformu; bulunan varyantın doğrulaması ve aile içi segregasyon analizi için Sanger dizileme tekniği kullanıldı. Karyotip ve moleküler sitogenetik analiz sonuçları normaldi, potansiyel kromozomal anomaliler ve mozaiklik dışlandı. Tüm ekzom veri analizinde, *ZP1* geni 3. ekzonunda (NM_207341.4, c.628C>T; p.Q210*) bilinen, nadir, anlamsız bir patojenik homozigot varyant tanımladı. Segregasyon çalışmasında birinci derece kuzen olan ebeveynlerinin bu varyant için heterozigot oldukları bulundu. Erken durdurma kodonu bileşimindeki bu mutasyon, ZP1 reseptör proteininin kısa sentezlenmesine neden olmaktadır. Zona pellusida, oositleri çevreleyen ve dört tip reseptör proteini (ZP1-4) içeren temel bir glikoproteindir. Bu çalışma, tespit edilen homozigot varyantın oosit matürasyon defekti ve kadın infertilitesi ile ilişkili olduğunu gösteren ilk olgu sunumudur. Ayrıca, ekzom dizileme yönteminin infertilite gibi karmaşık, multigenik durumlarda genetik etiyolojiyi belirlemek için kullanılabilecek değerli bir yöntem olduğu görülmüştür.

Anahtar Kelimeler: OOMD, zona pellusida, ZP1, kadın infertilitesi, ekzom dizileme

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INTRODUCTION

Oocyte maturation defect (OOMD) is a rare condition that occurs due to disruptions in the maturation process of oocytes and leads to primary female infertility, which is diagnosed mainly during assisted reproduction techniques (ART) (1). Twelve genes related to OOMD have been identified, and both autosomal dominant and recessive inheritance have been observed (*ZP1, TUBB8, ZP3, PATL2, WEE2, ZP2, PANX1, BTG4, TRIP13, REC114, ASTL, FBXO43*).

ZP1 pathogenic gene variants lead to OOMD with AR inheritance in homozygous or compound heterozygous form. Deletions leading to a frameshift and protein truncation causing variants (c.170-174del, c.507del, c. 508del, c.1129-1130del, c.1169-1176del), splice-site variants (c.1014+1G>A, c.1430+1G>T, c.1775-3C>A), missense variants (c.181C>T, c.1228C>T, c.1708G>A) and nonsense mutations (c.1413G>A, c.1510C>T, c.1663C>T) have been reported (2-8). Here, we present a female primary infertility case with four unsuccessful ART trials due to empty follicle syndrome and OOMD, and who has a homozygous nonsense variant in the *ZP1* gene.

MATERIAL and METHODS

Karyotyping, FISH analysis, and whole exome sequencing (WES) were performed. The xGen Exome Research Panel IDT Kit was used for library preparation, and the proband's sample was sequenced on the Illumina NextSeq® platform. An average reading depth of 65x was obtained for the target exome regions. The data were aligned with the reference genome data using the Burrows-Wheeler Aligner, and the shooting of the variants was done with the GATK Unified Genotyper. The alignment corrections in the in/del regions with realignment and filtering processes were carried out according to the percentage of variant detection (≥30%) and reading depth (≥10x). Sanger sequencing was performed for confirmation and segregation studies. Sequence data were analyzed using Seq Scape v3 and Chromas v2.6.6 analysis programs.

The bioinformatics analysis started with creating a list of active pathway genes through data mining, and genes related to female infertility were examined as the first filtering step. Secondly, variants classified as pathogenic or likely pathogenic were evaluated (≥20x of reading depth, minor allele frequency (MAF) of <0.01). The variant analysis criteria from the American College of Medical Genetics and Genomics (ACMG) were considered (9). Varsome and GnomAD databases were used for *in silico* analysis. This study was approved by Istanbul Faculty of Medicine Clinical Research Ethics Committee (Date: 09.02. 2018, No:249). The case and family members both signed the informed consent form. This study was funded by the Scientific Research Projects Coordination Unit of Istanbul University (Grant number: TSA-2018-32135).

RESULTS

The 31-year-old patient was referred to Istanbul University, Istanbul Faculty of Medicine, Department of Medical Genetics, to clarify the genetic etiology. Her parents were first cousins. Her pubertal development was normal, and anatomical, endocrinological, and autoimmune defects were excluded. Her physical examination was normal, but short stature with -3 SD was observed with limited extension flexion on bilateral elbows. Bilateral proximal radioulnar synostosis and slightly short ulnas were detected on the radiograph. Four ART trials were done, but follicles never achieved maturation.

Initially, chromosome analysis was investigated and revealed 46,XX karyotype. To exclude monosomy X mosaicism and *SHOX* gene deletion, fluorescence in-situ hybridization (FISH) using X chromosome centromeric (DXZ1) and SHOX-probe (SHOX/SE X) (CytoCell, Cambridge, UK) on interphase nuclei of lymphocytes and mucosal cells was performed and the result was normal. WES data analysis identified a known, rare, nonsense pathogenic homozygous variant in exon 3 (NM_207341.4, c.628C>T; p.Q210*) in the the OOMD-associated ZP1 gene. This variant was classified as pathogenic according to the ACMG criteria. This variant's frequency is 0.000008508 in heterozygous form, according to the gnomAD database. Sanger sequencing studies were performed with DNA obtained from the peripheral blood of first-degree cousin parents of the patient. They were both carrier for this variant (Figure 1).

DISCUSSION

ZP1 protein and three other zona pellucida proteins form the zona pellucida. This thick glycoprotein layer is effective in oocyte maturation, sperm binding at fertilization, acrosome reaction initiation, polyspermy inhibition after fertilization, and preimplantation embryo protection (10). The proteins in the zona pellucida complex are synthesized independently of each other and transported to the cell surface by the endomembrane system. Cross-links formed by ZP1 proteins also form connections in the complex (2). Supporting this, in the studies conducted with mice without ZP1 protein, zona pellucida formed lankly around oocytes, and reproductivity was reduced (11).

The *ZP1* gene, located on the long arm of chromosome 11 (11q12.2), contains 12 exons. The encoded protein has seven domains: signal peptide (SP; the residues of 1-26), ZP-N1 domain (36-138), P-type Trefoil domain (232-277), ZP-N domain (277-380), ZP-C domain (402-522), Consensus furin cleavage site (CFCS; 522-525) and transmembrane domain (TM; 602-624). The absence of zona pellucida can be observed under the microscope in unsuccessful ART trials. Homozygous variants of the *ZP1* gene with autosomal recessive inheritance (MIM_615774)

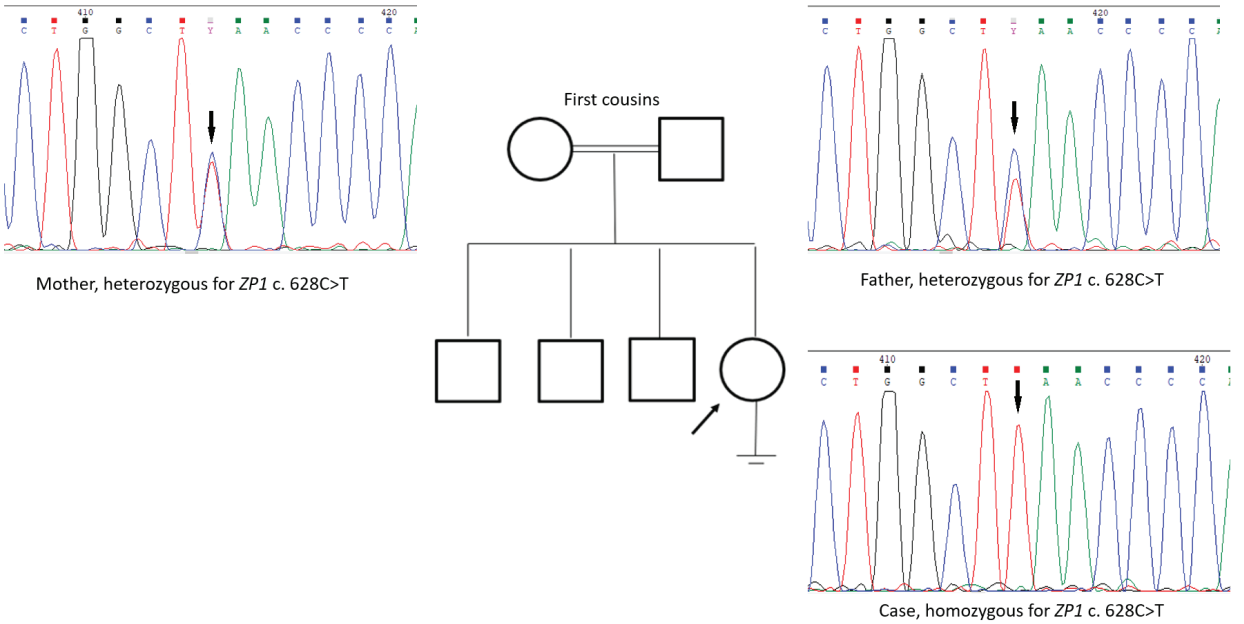

Figure 1: Confirmation and segregation of the ZP1 variant. Proband was homozygous for the *ZP1* c.628C>T variant, and her parents, who were first cousins, were detected as carriers.

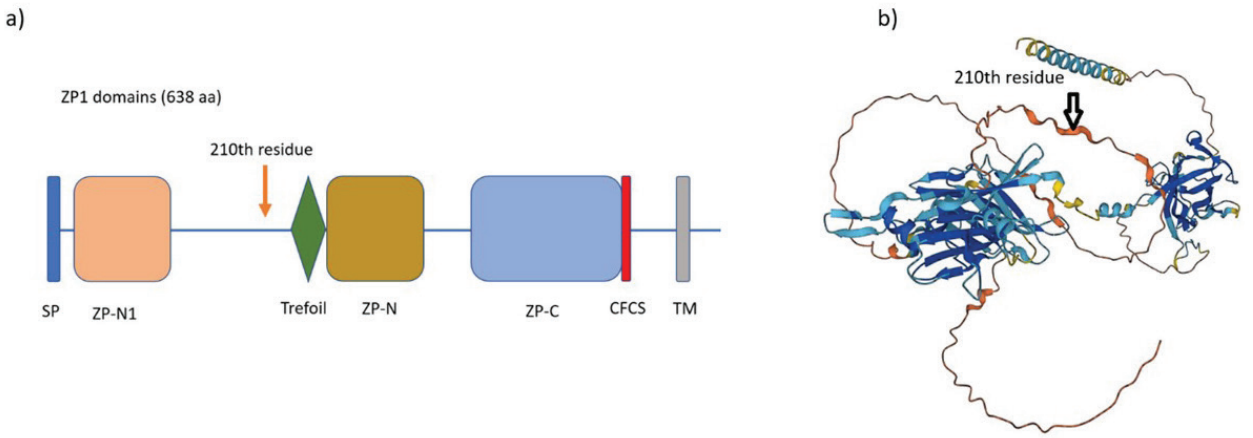

Figure 2: ZP1 protein domains and the location of the detected variant a) Nonsense mutation in ZP1 leading to truncated protein at the 210th residue. This results in the loss of trefoil (1-26), ZP-N (277-380), ZP-C (402-522), CFCS (522-525), and TM (602-624) domains. SP: signal peptide, CFCS: consensus furin cleavage site, TM: transmembrane **b)** The position of the 210th residue in ZP1 protein's 3D structure (AF-P60852-F1)

are related to OOMD-1. Our variant was in the 3rd exon and affected the protein between the ZP-N1 and Trefoil domains. All other domains were lost except for the signal peptide ZP-N1 domain due to premature protein termination (Figure 2).

In our case, empty follicle syndrome and oocyte maturation defect were diagnosed during ART trials. The detected variant was classified as pathogenic according to the ACMG and segregated in the family. The case's brothers weren't investigated for this variant due to not accepting to join the study. The mother and father of the proband were heterozygous carriers for the same variant. This article is the first report that shows homozygous c.628C>T (p.Q210*; rs776515172) mutation associated with OOMD. We conclude that exome data analysis is an efficient tool for identifying the mutations and genes related to infertility.

Ethics Committee Approval: This study was approved by Istanbul Faculty of Medicine Clinical Research Ethics Committee (Date: 09.02. 2018, No:249).

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CASE REPORT / OLGU SUNUMU
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MULTIPLE BLADDER STONES AND SEVERE URETHRAL INJURY IN A PATIENT WITH ACUTE ABDOMEN: A CASE REPORT

AKUT KARIN TABLOSUNDAKİ BİR HASTADA ÇOKLU MESANE TAŞLARI VE AĞIR ÜRETRA YARALANMASI, OLGU SUNUMU

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ABSTRACT

Bladder stones are very common in the elderly population with lower urinary tract obstruction, and they are associated with adverse outcomes such as recurrent infections and lower urinary tract obstruction. Managing bladder stones has traditionally been done using open procedures such as a cystolithotomy or endoscopic removal. The objective of the study is to present a rare case of multiple bladder stones in a surgical emergency where urinary diversion was mandatory, as endoscopic manipulation appeared impossible for an 85-year-old man who presented with acute abdomen symptoms, hemodynamically unstable severe urethral injury, and multiple bladder stones. Abdominopelvic non-contrast computerized tomography showed free fluid in the abdomen, gas in the bladder, and numerous bladder stones. Emergency surgery was performed on the patient, and the preexisting perforated stomach ulcer was surgically reconstructed. For urinary diversion, the decision was made to perform open cystolithotomy to eliminate more than 80 bladder stones of different shapes and sizes. We placed a urinary catheter using a Benique bougie and performed the cystostomy to open a second route.

Keywords: Bladder stones, urethral injury, acute abdomen

ÖZET

Mesane taşları, alt üriner sistem obstrüksiyonu olan yaşlı popülasyonda çok yaygındır ve tekrarlayan enfeksiyonlar ve alt üriner sistem obstrüksiyonu gibi olumsuz sonuçlarla ilişkilidir. Mesane taşlarının yönetimi geleneksel olarak sistolitotomi gibi açık tekniklerle veya endoskopik olarak çıkarılmasıyla yapılmaktadır. Çalışmanın amacı, çoklu mesane taşı olan ve endoskopik manüpulasyon yapılamadığından üriner diversiyon yapılması için acil cerrahi müdahale gerektiren nadir bir olgununun sunulmasıdır. Akut abdominal bulguları olan 85 yaşındaki erkek olgunun hemodinamik olarak stabil olmayan ağır üretral hasarı bulunmaktaydı. Abdominopelvik kontrastsız bilgisayarlı tomografide batında serbest sıvı, mesanede gaz ve çok sayıda mesane taşı görüldü. Acil cerrahiye alınan hastanın önceden var olan ve perfore olmuş mide ülserine müdahale yapıldı. Farklı şekil ve boyuttaki 80'den fazla taşın alınması için uygulanacak üriner diversiyonun açık sistolitotomi şeklinde yapılmasına karar verildi. Benique buji kullanılarak üriner kateter yerleştirildi ve ikinci bir yol açmak amacı ile sistostomi uygulandı.

Anahtar Kelimeler: Mesane taşları, uretral yaralanma, akut karın

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INTRODUCTION

Bladder calculi account for approximately 5% of patients presenting urinary stone disease. These stones are usually a consequence of foreign bodies, obstruction, or infection Bladder stones are more common in developing countries, with a higher prevalence in men than women at an approximate ratio of 10:1 (1-4). The main causes of secondary bladder calculi in men involve urinary tract infections, urethral stricture, benign prostatic hyperplasia, and intravesical foreign body (3).

The symptoms most commonly associated with bladder stones are frequent urination, hematuria (typically terminal), and dysuria/suprapubic pain, which becomes worse toward the end of micturition. Sudden movement and exercise may exacerbate these symptoms. Detrusor overactivity is found in over two-thirds of adult male patients with vesical calculi and is significantly more common in patients with larger stones (> 4 cm).

Iatrogenic injury is the most common type of urethral trauma and mostly occurs during urethral catheterization (5). The incidence of male urethral injury during transurethral catheterization is 13.4:1,000 catheters inserted (6). Injuries can occur as a result of the tip of the catheter creating a false passage or of the anchoring balloon being inadvertently inflated in the urethra (7).

CASE REPORT

An 85-year-old man was referred to a Department of Urology in an overall poor condition, with blue hands, severe abdominal pain, and hemodynamic instability. No diagnostic procedures related to abdominal pain were performed at the hospital from which he had been referred.

Urological examination showed severe urethrorrhagia. Catheterization was also unsuccessful, with the bladder appearing empty on palpation. In addition, the abdomen was diffusely painful on manual review. The ultrasound showed an empty bladder with echoes/calculi; however, the stomach contained a lot of free liquid. An urgent abdominopelvic non-contrast computerized tomography (NCCT) was performed immediately while the patient was hypotensive and hemodynamically unstable; he was put on dopaminergic and adrenergic drugs while being transported to the intensive care unit (Figure 1).

The abdominal and pelvic NCCT examination showed pneumoperitoneum and a large amount of free fluids in the abdominal cavity, with air in the bladder and multiple bladder stones. The aboratory examination showed slightly increased CRP 54 mg/L, but surprisingly normal levels of WBC ($4.3x10^3$), RBC ($4.64x10^6$), Hgb (142 g/L), glucose (10.8 mmol/L), urea (9.9 mmol/L), creatinine (174 mmol/L), albumin (22 g/L), total protein (49 g/L), chloride

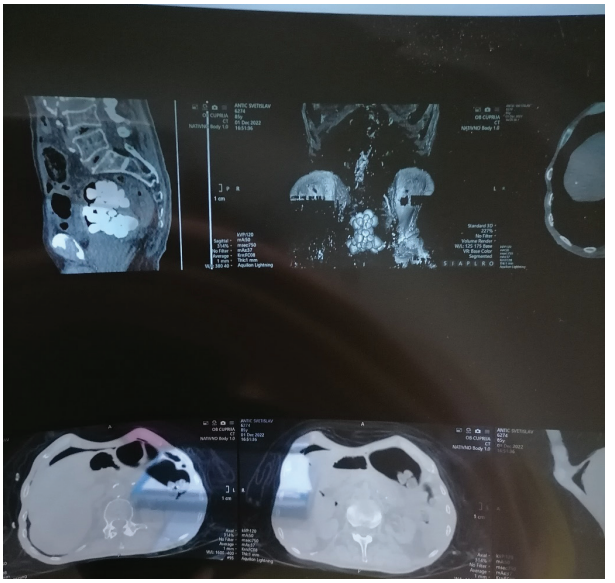

Figure 1: Initial preoperative abdominopelvic CT shows multiple bladder stones

(108 mmol/L), calcium (1.98 mmol/L), and potassium (4.8 mmol/L). Due to the worsening of the patient's hemodynamic condition, the decision was made to perform emergency surgery.

After the median exploratory laparotomy, a hemorrhagic and perforated stomach ulcer was identified and surgically repaired. Because the NCCT showed gas in the bladder, the bladder wall was opened to make a cystolithotomy. With the help of this procedure, more than 84 stones of different shapes and sizes were removed. Urinary diversion was established using the cystostom. A second catheter was introduced into the bladder using a Benique bougie through the completely injured urethra in order to establish early urethral realignment. The calculi that were manually eliminated from the bladder (a total of 84 as counted by staff) are shown in Figure 2, with many of the small ones missing. The urethra was not sutured due to potential hemorrhage of the prostate.

The surgery was followed by triple antimicrobial stewardship, dopaminergic and adrenergic stimulation, proton pump inhibitors, and thromboprophylaxis according to the Emergency Use Authorization (EUA) protocol (13).

DISCUSSION

The urethral injury had been followed by severe urethrorrhagia, which eliminated early endoscopic management as an option due to the overall poor condition and HD instability. Classical catheterization of the urethra was unsuccessful. Cystofix cystostomy was contraindicated as a result of the bladder being empty due to acute kidney injury. Retrograde urethrography was postponed due to the patient's instability (8, 9). Contrast-enhanced NCCT was not performed due

Figure 2: The postoperative picture shows the majority of extracted bladder calculi, in particular the largest ones.

to azotemia and haemodynamic instability.

The patient immediately underwent median laparotomy to explore the abdominal cavity. A large amount of free purulent fluid was removed. Further exploration showed an old stomach perforation with hemorrhage. A large amount of free fluid was found in the liver and spleen. Perforation was managed surgically.

The bladder was opened along the middle line, followed by the extraction of gas and many bladder stones (Figure 2). The staff counted 84 stones of different sizes and shapes, many of which are shown in Figure 2. Due to complete urethral injury, the Benique technique for Foley catheter placement was used to set the urinary diversion to make an early realignment of the urethra (11, 12). Haemodynamic instability was one of the reasons for not suturing the urethra. Urinary diversion was ensured by placing a cystostomy catheter. The bladder was then surgically closed.

Postoperatively, three broad-spectrum antibiotics were administrated, as well as corrections to the electrolyte and metabolic disbalance due to renal insufficiency. Post-operative follow-up was performed every day with blood and gas analyses. The early realignment of the urethra without suturing allowed the urethral injury to be decently managed, as this facilitated manual re-catheterization seven days after surgery.

A cystography was performed eight days post-surgery. No leaking of urine had occurred regarding the cystography, nor was any other extravasation of iodine contrast found from the bladder (14).

The data and literature search involved the use of PubMed to identify similar articles involving case reports and review articles. Some of these have been included in the full article.

CONCLUSION

Urethral injury due to incorrect catheterization is widespread in urological practice. The presence of massive and/or multiple bladder stones can affect catheterization and lead to urethral injury. Bladder stones and urethral injury require urinary diversion. In an ordinary situation, urethral injury indicates a retrograde urethrogram (RUG) or previous attempt at catheterization with endoscopic realignment. In the case presented in this study, the acute abdomen indicated the need for open surgical exploration and cystostomy with transurethral catheterization, further delaying treatment.

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A RARE CASE OF RENAL CLEAR CELL CARCINOMA ACROMETASTASIS AND ITS MANAGEMENT

NADİR BİR RENAL BERRAK HÜCRELİ KARSİNOM AKROMETASTAZI OLGUSU VE OLGUYA YAKLAŞIM

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ABSTRACT

Metastases that affect the distal regions of the upper and the lower extremities are called acrometastases and they affect the bones and the overlying tissues. Various cancer types may have single or multiple acrometastases. A sixty-four-year-old female patient had a painful and enlarging mass at the tip of the fifth digit of her right hand. The lesion appeared as a red macule at the junction between the nail plate and the hyponychium. The patient was in her seventh postoperative year after a left-sided radical nephrectomy with a histopathological diagnosis of renal clear cell carcinoma. Due to multiple metastases to the spleen and left femoral head, she had been treated with twenty sessions of radiotherapy and she was under nivolumab therapy twice a month for two years. A punch biopsy revealed a gland forming, CD 10, PAX 8 and vimentin-positive renal clear cell carcinoma metastasis. The patient was treated with amputation of the distal phalanx. Although rare, acrometastasis should be included in the differential diagnosis of patients with a history of renal clear cell carcinoma.

Keywords: Acrometastasis, amputation, hand, phalanx, renal clear cell carcinoma

ÖZET

Üst ve alt ekstremitenin distal kısımlarını etkileyen metastazlara akrometastaz denir ve bu tabloda, kemikler ve üzerlerindeki dokular etkilenir. Farklı kanser türleri tekli veya çoklu akrometastazlar yapabilir. Altmış dört yaşındaki bir kadın hasta, sağ elinin beşinci parmağının ucunda ortaya çıkan ağrılı ve sürekli büyüyen bir kitle ile polikliniğe başvurmuştur. Lezyon, tırnak plağı ve hiponişyum kesişimindeki kırmızı bir maküldür. Hasta, yedi yıl önce histopatolojik tanısı renal berrak hücreli karsinom olan bir kitle nedeniyle sol taraflı radikal nefrektomi geçirmiştir. Hastanın dalağında ve sol femur başında çoklu metastazları olduğundan hastaya yirmi seans radyoterapi uygulanmıştır. Hastaya son iki yıldır, ayda iki kez nivolumab tedavisi verilmiştir. Yapılan punch biyopside CD 10, PAX 8 ve vimentin pozitif olan ve gland oluşturan renal berrak hücreli karsinom metastazı saptanmıştır. Hastaya distal falanks ampütasyonu ameliyatı yapılmıştır. Renal berrak hücreli karsinom öyküsü olan hastalarda görülen parmak lezyonlarının ayırıcı tanısında, nadir de olsa akrometastaz göz önünde bulundurulmalıdır.

Anahtar Kelimeler: Akrometastaz, amputasyon, el, falanks, renal berrak hücreli karsinom

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INTRODUCTION

The metastases that affect the distal regions of the upper and the lower extremities are called acrometastases and they affect the bones and the overlying tissues (1). Acrometastasis is a very rare entity and it comprises only 0.1 % of all metastases (2). Various cancer types such as lung, colorectal, breast and genitourinary cancer may have single or multiple acrometastases (2, 3). Although this pathology can be seen in all genders and age groups, it is usually detected in the dominant hands of males (1, 4, 5).

Renal cell carcinoma accounts for 3% of all malignant lesions and approximately 400,000 new cases are diagnosed annually. Hand acrometastasis may be seen in 0.1% of patients with renal cell carcinoma (5-8). In this case report, a patient with a single renal clear cell carcinoma acrometastasis to the right fifth distal phalanx and her treatment plan are presented.

CASE REPORT

A sixty-four-year-old female patient was referred to the Department of Plastic Reconstructive and Aesthetic Surgery by the Department of Medical Oncology. She had a painful and enlarging mass at the tip of the fifth digit of her right hand (Figure 1). The patient, with a dominant right hand, stated that she noticed the lesion which appeared as a red macule at the junction between the nail plate and the hyponychium three months ago.

The patient had a left-sided total nephrectomy due to a histopathological diagnosis of renal clear cell carcinoma (WHO/ISUP Grade 2) and she was in her seventh postoperative year. The patient did not have any distant metastases until her fifth postoperative year when multiple metastases were detected in her spleen and in her left femoral head. The multidisciplinary tumor board did not refer the patient for metastasectomy and she had been treated with twenty sessions of splenic and left femoral radiotherapy. A bimonthly nivolumab therapy was initiated and it was continued for two years.

After a detailed history and a thorough physical examination, right-hand radiographs were obtained and an osteolytic lesion at the dorsal aspect of the fifth distal phalanx was detected (Figure 2). A punch biopsy was performed at the hyponychium and it revealed a gland forming, CD 10, PAX 8 and vimentin-positive renal clear cell carcinoma metastasis (Figure 3). A positron emission tomography and computed tomography scan were performed and splenic, left femoral and right fifth distal phalangeal metastases were found.

The operative treatment of this acrometastasis did not aim for a survival benefit for the patient; however, palliation was planned due to the progressive pain and enlargement of the lesion. Amputation of the right fifth distal phalanx was performed and the specimen was sent to the Department of Pathology, confirming the initial diagnosis. The patient was referred to the Department of Medical Oncology and her symptoms were relieved right after the operation. She did not come for the clinical follow-ups one year after the amputation.

Figure 1: The lesion is seen as a red macule at the junction between the nail plate and the hyponychium of the right fifth digit.

Figure 2: An osteolytic lesion at the dorsal aspect of the fifth distal phalanx is seen in the lateral view of the direct radiograph.

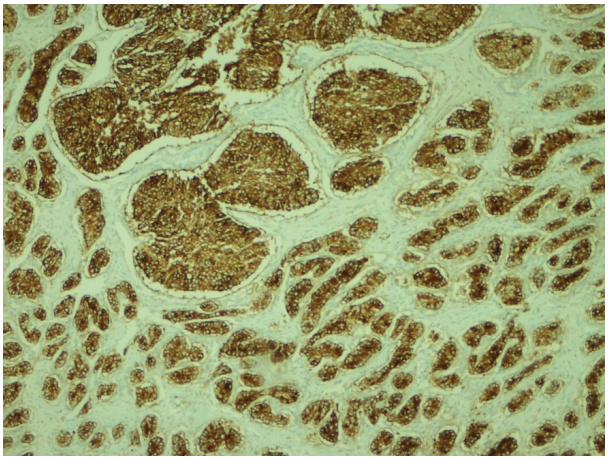

Figure 3: A gland forming, CD 10, PAX 8 and vimentin-positive renal clear cell carcinoma metastasis is demonstrated (200X magnification and Vimentin immunohistochemical staining).

The patient was informed about both the treatment and the study process and consent was obtained.

DISCUSSION AND CONCLUSION

The hand has many primary mass lesions; however, physicians should be aware of metastatic lesions that may mimic primary ones (4). Primary lesions of the hand such as lobular capillary hemangioma, angiokeratoma, acral lentiginous malignant melanoma, squamous cell carcinoma and basal cell carcinoma should be included in the differential diagnosis of acrometastasis (9). In order to reach a precise diagnosis, a detailed history and physical examination is mandatory. Direct radiographs and contrast-enhanced computed tomography may aid in differentiating among other pathological conditions; however, histopathological verification of either excisional or incisional biopsy specimens is mandatory for accurate diagnosis (9).

Flynn et al. reviewed the relevant literature and they found that the male patients had twice as many acrometastases than female patients (1). Also, they found that the mean age of patients with acrometastases was 58 years (1). The age of this patient is concordant with the literature despite her gender. Flynn et al. evaluated the primary tumors and they found that renal cancer is the second most common source of acrometastases (1). This patient had renal clear cell carcinoma as her primary tumor and this finding is similar to the literature. The distal phalanx is the most common host for acrometastases (1) as it was seen in this patient. In the literature, the fifth digit is the least affected part of the hand; however, the acrometastasis was at the fifth digit of this patient (1). Thus, a rare metastasis was seen at a rare anatomic site.

Although metastasectomy does not affect overall survival, all studies support operative treatment of the acrometastases unless the patient has a medical contraindication for surgery (1-5). In fact, amputations may help to alleviate the debilitating symptoms of the patients, enabling palliation and increasing the quality of life.

Clinicians should be vigilant about new acral lesions in patients with a history of cancer. Despite their rarity, acrometastases should be included in the differential diagnoses of patients with renal clear cell carcinoma and a multidisciplinary approach should be the mainstay of the treatment.

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