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BAGCILAR MEDICAL BULLETIN
Bağcılar Tıp Bülteni

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EDITORIAL

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Can Deceased People be Added as Authors on Academic Publications?

Ölen Kişiler Akademik Yayınlara Yazar Olarak Eklenebilir mi?

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Keywords: Authorship, death, literature, publications
Anahtar kelimeler: Edebiyat, ölüm, yayınlar, yazarlık

Introduction

In this issue of our journal, we published the article by Altun et al. (1) titled "Analysis of the knowledge level of the surgical residents regarding the preoperative assessment of the adult elective non-cardiac surgery patients with specific clinical condition". Nagihan Karahan, one of the authors of this article, passed away in 2023 (1). Based on this example, we wanted to inform our readers about the authorship of the publications of deceased persons.

This editorial underscores the importance of ethical considerations in posthumous authorship and provides a guideline for ensuring that contributions are recognized with the respect and transparency that they deserve. By adhering to these principles, the medical research teams can continue to honor the legacies of its contributors accurately and ethically (2).

Authorship in scientific and medical research extends beyond a mere acknowledgment of contribution; it serves as a testament to the intellectual and practical efforts of individuals involved in the study. The ethical and procedural dimensions of attributing authorship are well-defined for living contributors, but a unique question arises when considering deceased individuals. Can a deceased person be listed as an author of scientific articles? The answer is affirmative, contingent upon adherence to certain ethical standards and guidelines (3). This article explores the ethical and procedural aspects of attributing authorship to a deceased individual in scientific publications. Sometimes participants in research collaborations die before the research report is accepted for publication. Such an unfortunate event can occur at any stage of the work process from early idea and design to late changes in the manuscript, and even after the manuscript has been submitted to a journal. This situation may raise questions in our minds for both the authors and the editorial boards of the journals.

Opinions on this subject have a wide range. While some insistently argue that a deceased individual can never be listed as an author, others believe that such individuals should be thanked, and yet another group states that

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posthumous authorship is permissible given that the individual meets the established criteria for authorship (4).

Yes, a deceased person can be listed as an author of scientific articles under certain circumstances (2). This typically occurs when the individual made significant contributions to the research before their death. Assigning authorship to a deceased researcher involves careful consideration of ethical guidelines and respect for the individual's contributions. The key points are (3):

1.Significant contribution: The deceased person must have made a substantial intellectual contribution to the conception, design, execution, or interpretation of the research.

2.Manuscript drafting or revising: They should have been involved in drafting the manuscript or revising it critically for important intellectual content.

3.Approval of final version: If they contributed significantly but died before the final version was completed, it is generally acceptable to include them as an author, provided that the remaining authors believe they would have approved the final manuscript.

4.Ethical and transparent acknowledgment: The situation should be transparently communicated to the journal and readers. Often, a note is included in the manuscript acknowledging the contribution and noting the person's passing.

5.Institutional policies: Policies can vary by journal and institution, but most follow guidelines from bodies such as the International Committee of Medical Journal Editors, which emphasize the importance of substantial contributions and approval of the final version.

Precedents and Practical Examples

There are numerous precedents in medical research where deceased individuals have been rightfully credited as authors posthumously. These instances often occur in long-term studies where the deceased had laid significant groundwork. For example, in multi-year oncology studies or epidemiological research, the contributions of a deceased researcher can be substantial and ongoing until their death (5). The eleven journals under the umbrella of the American Meteorological Society adopt the view of designating a deceased person who meets the authorship requirements as a co-author (5). The corresponding author accepts responsibility for including as authors all individuals who meet these criteria for authorship. Since it is not considered appropriate for authors to thank each other in the Acknowledgments section of journals within the American Physical Society, it is advocated not to thank a deceased author (5). However, they can express their continued respect and admiration for a deceased co-author with a dedication, or a death dagger (†) and a footnote are placed in the author's line of the title page. In the footnote, it is stated that the author passed away and the date of death is provided for reference (4). Similarly, in the British Medical Journal; deceased persons who are deemed suitable as authors are included with a dagger symbol (†) next to the author's name and a footnote stating that the author has passed away and giving the date of death (6). Dove Press requests that one of the authors be appointed as proxy in cases where a posthumous author is appointed but submission forms must be signed. This proxy author should be addressed to the writer, a family member, or the person holding the power of attorney. In all cases, an effort should be made to contact the family of the deceased author to inform them of the intent and obtain their consent for the listing (6). As a general guideline at Cochrane, where an author has made a significant contribution to a protocol or review (sufficient to guarantee authorship) but has died before publication and co-authors consider it appropriate to include the deceased author in the byline, editorial teams will carry out this action and ensure that the author is included in the byline (2). Deceased persons who are eligible as Authors in more than two thousand seven hundred journals of the Springer Nature publishing house are included with a footnote announcing their death (5).

If the deceased author was the contact person for the scientific article, a new contact person should be determined (2).

Posthumous authorship in medical research is both ethically permissible and appropriate when the individual's contributions meet the established criteria for authorship (2). Transparent communication and adherence to ethical guidelines are essential to ensure that the recognition of the deceased's work is handled with respect and integrity. As medical research continues to evolve, corresponding adjustments in policies and practices surrounding this sensitive tissue are anticipated to ensure that all contributions are fairly and accurately acknowledged.

In conclusion, acknowledging the contributions of deceased researchers upholds the integrity of the scientific process and honors the lasting impact of their work. It is a testament to the collaborative and enduring nature of scientific inquiry.

Ethics

Authorship Contributions

Surgical and Medical Practices: K.E., M.A., Concept: M.A., Design: M.A., Data Collection or Processing: M.A., Analysis or Interpretation: M.A., Literature Search: M.A., Writing: M.A.

Conflict of Interest: No conflict of interest was declared by the authors.

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ORIGINAL RESEARCH

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Examination of Socio-demographic, Clinical and Laboratory Findings of Patients Hospitalized in Our Clinic with the Diagnosis of Rotavirus Gastroenteritis

Rotavirüs Gastroenterit Tanısı ile Kliniğimize Yatan Hastaların Sosyo-demografik Özellikleri, Klinik ve Laboratuvar Bulgularının İncelenmesi

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Abstract

Objective: Nowadays, viruses are the leading cause of acute gastroenteritis, while Rotavirus (RV) is the most common cause of acute viral gastroenteritis. In this study, the RV antigen positive diagnosis of gastroenteritis patients hospitalized in the pediatric service of the socio-demographic, clinical and laboratory features was aimed to be interpreted by comparison with literature data.

Method: Socio-demographic data of patients hospitalized with the diagnosis of RV gastroenteritis, clinical and laboratory findings were retrospectively evaluated the hospital's file was obtained from the records.

Results: The study of children hospitalized with acute gastroenteritis caused a mean age of 17.68 months from 740 patients who were enrolled, and 270 patients who were positive for RV and RV ratio was found to be 36%. Although the cases were most frequently seen in the spring, the most common months were February, March and April. The most frequent application causes were diarrhea and vomiting and the most common age group was the age group of 6 months-2 years of age. Five patients developed complications were detected. Laboratory findings in 101 patients with C-reactive protein positive (37.4%), 213 patients (78.8%) serum aspartate aminotransferase levels were high, in 94 patients (34.8%) had elevated alanine aminotransferase levels.

Conclusion: Most cases of gastroenteritis were admitted to the service accounted for RV diarrhea and especially important cause of diarrhea is seen in winter and spring seasons. Therefore, the RV detection in cases of gastroenteritis is important to predict patient's clinic and prevent unnecessary use of antibiotics.

Keywords: Child, gastroenteritis, Rotavirus

Öz

Amaç: Günümüzde, akut gastroenterit etkenleri arasında virüsler ilk sırada yer alırken, Rotavirüs (RV) ise akut viral gastroenteritlerin en sık etkenidir. Bu çalışma ile RV antijeni pozitif gastroenterit teşhisi ile çocuk servisinde yatırılan hastaların sosyo-demografik, klinik ve laboratuvar özelliklerinin literatür verileri ile kıyaslanarak yorumlanması amaçlandı.

Yöntem: RV gastroenteriti tanısı ile yatan hastaların sosyo-demografik verileri, klinik ve laboratuvar bulguları hastaneye ait dosya kayıtlarından geriye dönük incelenerek elde edildi.

Bulgular: Çalışmaya akut gastroenterit nedeni ile çocuk kliniğine yatırılan 740 hastadan yaş ortalaması 17,68 ay olan 270 RV pozitif saptanan olgu dahil edilmiş olup, RV oranı %36,5 olarak bulundu. Olgular en sık ilkbahar mevsiminde görülmekle birlikte en sık görüldüğü aylar ise Şubat, Mart ve Nisan ayları idi. En sık başvuru nedeni ishal ve kusma birlikteliği iken en sık görüldüğü yaş grubu 6 ay-2 yaş grubu idi. Beş hastada komplikasyon geliştiği tespit edildi. Laboratuvar bulgularından C-reaktif protein 101 hastada pozitif (%37,4), 213 hastada (%78,8) serum aspartat aminotransferaz düzeyi yüksek, 94 hastada (%34,8) alanin aminotransferaz düzeyi yüksek bulundu.

Sonuç: Servisimize yatırılan gastroenterit olgularının çoğunu RV ishalleri oluşturuyor olup, özellikle kış ve ilkbahar mevsimlerinde görülen önemli ishal nedenidir. Bu nedenle gastroenterit olgularında RV saptanması, hastanın kliniğinin öngörülmesi ve gereksiz antibiyotik kullanımının önüne geçilmesi bakımından önemlidir.

Anahtar kelimeler: Çocuk, gastroenterit, Rotavirüs

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Introduction

Rotavirus (RV) continues to be a significant viral pathogen, constituting a serious global health issue and leading to child deaths worldwide (1,2). Among viral agents causing acute gastroenteritis, RV is the most prevalent, with adenovirus being the second (3). Epidemiological data indicates that RV infections are the second leading cause of child deaths. In 2013, approximately 215,000 children worldwide died from RV-related diarrhea, with the majority of these deaths occurring in low-income countries (4). Epidemiological studies reveal that RV infections exhibit seasonal variations worldwide, often peaking during the winter months (5,6).

RV infections, particularly in developing countries, prominently contribute to acute diarrhea in children under the age of 2 and are recognized as a leading cause of dehydration due to acute diarrhea (7,8). A notable characteristic of RV diarrhea is the high rate of hospitalization associated with it (9). Globally, 40% of hospitalizations for severe diarrhea in young children are attributed to RV infections (10). While it is known to be associated with high mortality rates in developing countries, in developed nations, it is linked to high disease rates and economic burden (3).

This study aims to retrospectively analyze the socio-demographic, clinical, and laboratory characteristics of patients diagnosed with RV antigen-positive gastroenteritis who were admitted to the pediatric department over a 2-year period. The goal is to compare the results with existing literature and previous studies.

Materials and Methods

At the University of Health Sciences Turkey, Prof. Dr. Cemil Taşcıoğlu City Hospital, the medical records of 270 patients who were hospitalized for RV gastroenteritis diagnosis during a 2 year period (01.01.2012-31.12.2013) were retrospectively analyzed. The diagnosis of RV gastroenteritis was established using the qualitative immunochromatographic method (Simple/Stick Rota Adeno Operon, Spain) on fecal samples. Furthermore, bacterial agents such as *Vibrio cholerae, Salmonella, Shigella, Campylobacter, Yersinia enterocolitica,* etc., and parasitic agents were examined using standard microbiological methods. The patients who exhibited bloody findings in the macroscopic examination of fecal samples, showed the presence of parasites in laboratory analysis, and had bacterial growth detected in fecal cultures were excluded from the study. The patients were categorized into three groups based on their age: 0-6 months, 6-24 months, and over 24 months. The socio-demographic characteristics, clinical features, and laboratory findings of the patients were compared. The study was conducted in accordance with the principles of the Helsinki Declaration and received approval from the Ethics Committee of University of Health Sciences Turkey, Prof. Dr. Cemil Taşcıoğlu City Hospital with decision number 177 on February 25, 2014. The study was derived from the thesis titled “inpatients to our clinic with the diagnosis of RV gastroenteritis and socio-demographic, clinical and laboratory findings investigation”.

Statistical Analysis

In the evaluation of data obtained in the study, statistical analysis was performed using SPSS (Statistical Package for Social Sciences) version 15.0 and Graph Pad InStat demo version. In addition to descriptive statistical methods (such as mean, standard deviation, minimum, maximum), in the analyses comparing groups, categorical variables were assessed using the chi-square test and Fisher’s Exact test. For comparisons between two groups, Student’s t-test and Mann-Whitney U test were employed, while One-Way ANOVA (Analysis of Variance) was used for comparisons among three groups, followed by post-hoc Tukey test for pairwise comparisons and Kruskal-Wallis test followed by Dunn’s test. Pearson correlation test was used for assessing correlations. Results were evaluated at a significance level of $p<0.05$ with a confidence interval of 95% (*$p<0.05$, **$p<0.01$, ***$p<0.001$).

Results

In the study, 270 out of 740 patients who were admitted to the Pediatric Clinic of University of Health Sciences Turkey, Prof. Dr. Cemil Taşcıoğlu City Hospital, with complaints of acute diarrhea were included, and they were diagnosed with RV gastroenteritis (36.5%). The ages of the patients ranged from 1 month to 116 months, with 58.9% (n=159) being male and 41.1% (n=111) female. Regarding the presenting complaints, 64.8% (n=175) had diarrhea and vomiting, 18.1% (n=49) had diarrhea, vomiting, and fever, 9.6% (n=26) had only diarrhea, 7% (n=19) had diarrhea and fever, and 0.4% (n=1) had only vomiting. During the follow-up of hospitalized patients, 48.5% (n=131) had a temperature below 37.5 °C, 25.9% (n=70) had a temperature between 38-39 °C, 22.6% (n=61) had a temperature between 37.5-38 °C, and 3% (n=8) had a temperature above 39 °C (Table 1).

When examining the seasonal distribution of cases, 35.9% (n=97) were observed in spring, 31.1% (n=84) in winter, 18.1% (n=49) in autumn, and 14.8% (n=40) in summer (Figure 1). By monthly distribution, cases were as follows: 13.3% (n=36) in February-March-April, 12.2% (n=33) in January, 9.3% (n=25) in May-October, 8.1% (n=22) in June, 5.6% (n=15) in December, 4.8% (n=13) in November, 4.1% (n=11) in September, and 3.3% (n=9) in July-August (Figure 2). Among the patients, 62.6% (n=169) had negative C-reactive protein (CRP), while 37.4% (n=101) had positive CRP.

Regarding the biochemical values of the patients, the average urea level was 27.66±13.86 mg/dL (ranging from 3 to 92, median: 26), the average creatinine level was 0.30±0.13 mg/dL (ranging from 0.05 to 0.86, median: 0.28), the average sodium level was 136.14±4.11 mmol/L (ranging from 125 to 154, median: 136), the average potassium level was 4.29±0.57 mmol/L (ranging from 2.60 to 6.10, median: 4.20), the average aspartate aminotransferase (AST) level was 55.46±30.40 IU/L (ranging from 20 to 323, median: 48), and the average alanine aminotransferase (ALT) level was 35.84±30.93 IU/L (ranging from 6 to 366, median: 29).

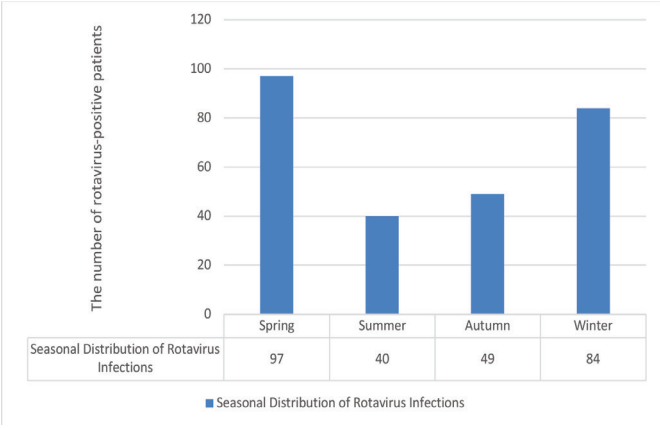

Figure 1. Seasonal distribution of Rotavirus infections

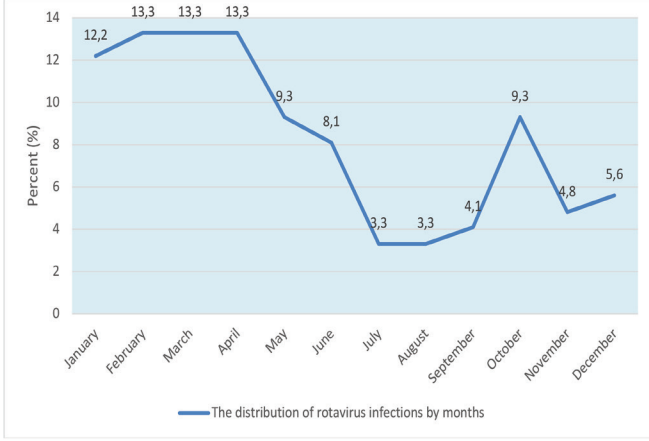

Figure 2. The distribution of Rotavirus infections by months

Table 1. The gender and symptoms of patients hospitalized due to Rotavirus based on age groups

	<6 months		6-24 months		>24 months		chi-square	p
	n	%	n	%	n	%		
Gender								
Male	41	65.1	86	58.1	32	54.2	1.562	0.458
Female	22	34.9	62	41.9	27	45.8		
Symptoms								
Diarrhea	17	25.8	8	5.5	1	1.7	-	**0.0001*** **
Vomiting	0	0.0	1	0.7	0	0.0		
Diarrhea-vomiting	32	48.5	100	69.0	43	72.9		
Diarrhea-fever	10	15.1	6	4.1	3	5.1		
Diarrhea-vomiting-fever	7	10.6	30	20.7	12	20.3		
Fever								
<37.5 °C	34	54.0	77	52.0	20	33.9	-	
37.5-38 °C	18	28.6	28	18.9	15	25.4		**0.034***
38-39 °C	10	15.9	40	27.0	20	33.9		
>39 °C	1	1.6	3	2.0	4	6.8		
Rotavirus related complications								
None	60	95.2	147	99.3	58	98.3	4.070	0.131
Present	3	4.8	1	0.7	1	1.7		
Source of Rotavirus								
Community	50	79.4	125	84.5	54	91.5	3.530	0.171
Nozocomial	13	20.6	23	15.5	5	8.5		

*: p<0.05, ***: p<0.001, n: Number of patients, %: Column percent

Table 2. Laboratory characteristics of patients hospitalized due to Rotavirus

	Mean	SD	Median	Min	Max
WBC (10^3/mm^3)	10.51	4.20	10.00	1.73	27.70
Hemoglobin (g/dL)	11.49	1.32	11.50	6.60	14.72
Hematocrit (%)	34	4	34	20	47
MCV (fL)	78.41	8.26	78.30	52.40	102.00
PC (10^3/µL)	365.64	122.11	359.60	27.80	808.80
NC (10^3/µL)	6.26	4.22	5.75	0.31	22.25
% Neutrophils	56.57	22.04	57.50	3.00	95.00
% Lymphocyte	31.48	19.40	28.50	1.00	78.00
% Monocyte	10.22	6.07	9.00	1.00	67.00
MPV (fL)	7.65	0.90	7.48	5.60	11.94
PDW (%)	16.31	0.64	16.30	12.91	19.00
RDW (%)	14.89	1.77	14.80	11.50	23.17
CRP (mg/L)	13.40	23.58	5.30	1.00	170.00
Urea (mg/dL)	27.66	13.86	26.00	3.00	92.00
Creatinine (mg/dL)	0.30	0.13	0.28	0.05	0.86
Na (mmol/L)	136.14	4.11	136.00	125.00	154.00
K (mmol/L)	4.29	0.57	4.20	2.60	6.10
AST (IU/L)	55.46	30.40	48.00	20.00	323.00
ALT (IU/L)	35.84	30.93	29.00	6.00	366.00

SD: Standard deviation, WBC: White blood cell count, MCV: Mean corpuscular volume, NC: Neutrophil count, RDW: Red cell distribution width (%), PC: Platelet count*1000, PDW: Platelet distribution width (%), MPV: Mean platelet volume (fL), CRP: C-reactive protein, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase

Among the patients, 78.8% (n=213) had elevated serum AST levels, and 34.8% (n=94) had ALT levels above the upper limit of normal (Table 2).

In those aged below 6 months, the complaint of vomiting was significantly lower compared to those aged 6-24 months and those above 24 months ($p<0.001$). Among those aged over 24 months, the rate of having a fever below 37.5 °C was significantly lower compared to the other two age groups ($p=0.034$, $p<0.05$). Among those aged over 24 months, the length of hospital stay was significantly shorter compared to the other two age groups ($p=0.003$).

Discussion

RV infection is a leading cause of diarrhea-related morbidity and mortality globally among children under the age of 5 (11). Each year, RV gastroenteritis leads to the hospitalization of 2 million children and causes an average of 440,000 child deaths (12). Research related to etiology is of importance for diagnosis, treatment, and prognosis, as identifying viral agents can help prevent unnecessary antibiotic use.

In our study, the prevalence of RV among patients hospitalized for gastroenteritis was 36.5%. When looking at studies abroad, a study in Spain from 2001 to 2005 found a prevalence of 17.1% in children under 5 years of age hospitalized with gastroenteritis (13). In India, a study of children under 5 years hospitalized from 2009 to 2011 found a RV frequency of 35.9% (14). When we look at our country, in a study conducted by Ilktac et al. (15) in Istanbul between 2006-2010, 11711 cases of acute gastroenteritis were examined, and the prevalence of RV was found to be 15.5%. In a study conducted by Konca et al. (16) between March 2012 and February 2013, they determined the prevalence of RV to be 16.5%. In Turkey, studies in different cities and periods, predominantly focusing on the age group of 0-5 years, have reported significantly different RV positivity rates. In our study, which included only hospitalized children, the RV positivity rate was higher at 36.5%.

Although the cause is not known, the seasonal nature of RV diarrhea is well established (2). In temperate climates, RV peaks during the winter months (17). In our study, the seasonal distribution showed that RV gastroenteritis cases were observed in 35.9% in spring, 14.8% in summer, 18.1% in autumn, and 31.1% in winter. The months with the highest incidence of RV diarrhea were February (13.3%), March (13.3%), and April (13.3%), followed by January (12.2%)

and May (9.3%), October (9.3%). A multicenter prospective study in Europe conducted in 2004-2005 similarly found that diarrheal cases occurred most frequently between October and May, with a peak in January to March (18). Studies in Spain also found a higher incidence during the winter months (13). Carneiro et al. (19) conducted a study involving 218 cases of children aged 0-19 years who were hospitalized in Brazil due to severe RV infections. In their research, they examined the clinical and epidemiological findings of these cases. They found that RV-positive cases were most commonly observed in the months of June and July (19). In contrast to many other studies, the reason for the high prevalence of RV gastroenteritis during the summer months in this study was attributed to the unique tropical climate in Brazil. Unlike in other countries where RV is more frequently detected during rainy seasons in winter, in Brazil, it is observed during the summer months due to the specific characteristics of the climate (19).

When examining the clinical features of RV diarrheas, fever, diarrhea, and vomiting are the most common symptoms, either alone or in combination (20). In our study, the most common complaint was diarrhea-vomiting (73.4%), followed by diarrhea-vomiting-fever (16.6%). Only 7.4% of patients presented with diarrhea alone. This may indicate that families are more concerned about vomiting. Additionally, patients under 6 months of age had a significantly lower rate of vomiting as their presenting complaint compared to those aged 6-24 months and over 24 months ($p<0.001$). This observation is consistent with the literature, which suggests that milder infections in the first 6 months are related to transplacental transfer of maternal antibodies and breastfeeding (21). In our study, it was found that the hospital stay was significantly shorter in individuals aged over 24 months compared to the other age groups of 0-6 and 6-24 months. The shorter hospital stay after 24 months of age can be attributed to the natural course of previously experienced infections, which reduces the incidence and severity of subsequent episodes.

After RV infections, viremia can lead to extraintestinal involvement (22). In Taiwan, a study conducted by Wu et al. (23) comparing the clinical characteristics of RV and norovirus gastroenteritis found that AST and ALT levels were higher in cases of RV gastroenteritis. Similarly, in studies by Akelma et al. (24), which covered the years 2005 to 2012 and included 272 patients with confirmed RV infection, it was reported that 42% (15.4%) of the patients had elevated ALT levels, and 69% (25.4%) had elevated AST levels. In our study, 78.8% of the 270 patients had elevated serum AST levels, with an average AST level of 55 IU/L (range: 20-323 IU/L). Serum ALT levels were elevated in 34.8% of the cases, with an average ALT level of 36 IU/L (range: 6-366 IU/L).

Kang et al. (25) retrospectively examined 755 patients with RV infections between 1999 and 2011 and identified 17 patients (2.2%) with febrile seizures and 42 patients (5.5%) with afebrile seizures. In a retrospective study by Hung et al. (26) covering a 10-year period and including 1937 patients with RV gastroenteritis, 40 patients (2.06%) were observed to have afebrile seizures. In our study, convulsions were observed in 2 patients, constituting 0.7% of all patients. In a study conducted by Scheier and Aviner (27) which included 632 patients hospitalized for RV gastroenteritis between May 1999 and May 2010, sepsis was detected in 2 patients (0.32%). In a study by Gözmen et al. (28), among 376 cases of RV gastroenteritis, bacteremia was found in 5 patients (1.3%). In our study, sepsis was observed in 2 patients, constituting 0.7% of all patients.

Study Limitations

The single-center and retrospective nature of our study are limitations. Additionally, the fact that the vaccination status of patients regarding RV was not queried constitutes another limitation of our study. We believe that conducting multi-center, prospective studies would contribute significantly to the understanding of the topic.

Conclusion

The detection of RV, the most common cause of diarrhea in children, is crucial not only for understanding the causative agent but also for predicting the patient's clinical condition and determining the appropriate treatment approach. Additionally, it plays a significant role in contributing to epidemiological knowledge. Identifying the causative agent can help prevent unnecessary antibiotic use and promote the expansion of vaccination programs that have been reintroduced.

Providing the appropriate approach to childhood diarrhea and evaluating the potential benefits of RV vaccines require each country to have its own data. Therefore, in Turkey as well, there is a need to determine the estimated rates of RV diarrhea and the clinical and epidemiological characteristics of the disease. This information is vital for healthcare decision-makers and public health officials to make informed choices regarding prevention and control strategies.

Ethics

Ethics Committee Approval: The study was conducted in accordance with the principles of the Helsinki Declaration and received approval from the Ethics Committee of University of Health Sciences Turkey, Prof. Dr. Cemil Taşcıoğlu City Hospital with decision number 177 on February 25, 2014.

Informed Consent: Not necessary for this manuscript.

Authorship Contributions

Concept: B.Y., M.T.K., F.K., K.P., V.A., Design: B.Y., M.T.K., F.K., K.P., V.A., Data Collection or Processing: B.Y., F.K., K.P., V.A., Analysis or Interpretation: B.Y., M.T.K., V.A., Critical Revision of Manuscript: B.Y., V.A., M.T.K., K.P., Final Approval and Accountabilty: B.Y., M.T.K., F.K., V.A., Supervision: B.Y., M.T.K., Writing: B.Y., M.T.K., F.K., V.A.

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ORIGINAL RESEARCH

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Effect of Iron Deficiency Anemia on Fetal and Maternal Morbidity

Demir Eksikliği Anemisinin Fetus ve Anne Morbiditesi Üzerine Etkisi

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Abstract

Objective: To investigate the effect of third-trimester iron deficiency anemia on fetal and maternal morbidity.

Method: A total of 240 pregnant women whose third trimester hemoglobin level was found to be <11 g/dL in the retrospective review of medical records were included in the study. Pregnant women who had blood samples taken at least twice for the diagnosis of anemia in the third trimester constituted the study group. Pregnant women whose gestational weeks were matched and without anemia were included as the control group. Multivariate logistic regression analysis was performed to identify independent risk factors for anemia after adjusting for age and body mass index (BMI).

Results: The rates of cesarean delivery, preterm labor, placental abruption, premature membrane rupture, low birth weight, and admission to intensive care due to fetal distress were significantly higher in the anemic group than in the non-anemic group. Vaginal birth rates in the anemic group (29.2%) were significantly lower than those in the non-anemic group (50%). While 170 patients in the anemic group underwent cesarean section (70.8%), 120 patients in the non-anemic pregnant group underwent cesarean section (50%). Logistic regression analysis revealed that high gravidity (95% confidence interval 1.176-2.677), parity (95% confidence interval 1.138-2.033), and gestational weeks (95% confidence interval 1.003-1.006), were independent risk factors for anemia severity after adjustment for potential confounders, including age and BMI.

Conclusion: Anemia during pregnancy increases cesarean delivery rates and decreases vaginal birth rates. Gravidity, parity, and gestational age increase the severity of anemia regardless of age and BMI. Treating anemic pregnant women with iron supplementation may reduce cesarean section rates and increase normal birth rates in a more cost-effective manner.

Keywords: Cost effectivity, feto-maternal morbidity, iron deficiency anemia, third trimester

Öz

Amaç: Üçüncü trimester gebelerde demir eksikliği anemisinin fetal ve maternal morbidite üzerine etkisini araştırmak.

Yöntem: Tıbbi kayıtların retrospektif olarak incelenmesinde üçüncü trimester hemoglobin düzeyi <11 g/dL olan 240 gebe çalışmaya dahil edildi. Üçüncü trimesterde anemi tanısı için en az iki kez kan örneği alınan gebeler çalışma grubunu oluşturdu. Gebelik haftaları uyumlu, anemisi olmayan gebeler kontrol grubu olarak alındı. Yaş ve vücut kitle indeksi (VKİ) ile ayarlama yapıldıktan sonra anemi için bağımsız risk faktörlerini belirlemek amacıyla çok değişkenli lojistik regresyon analizi yapıldı.

Bulgular: Sezaryen doğum, erken doğum, plasentanın ayrılması, erken membran rüptürü, düşük doğum ağırlığı ve fetal distres nedeniyle yoğun bakıma alınma oranları anemik grupta anemik olmayan gebelere göre anlamlı olarak daha yüksekti. Anemik grupta vajinal doğum oranları (%29,2), anemik olmayan gruba (%50) göre anlamlı derecede düşüktü. Anemik grupta 170 hastaya (%70,8) sezaryen yapılırken, anemik olmayan gebelerde 120 hastaya (%50) sezaryen uygulandı. Lojistik regresyon analizi, yüksek gravidanın (%95 güven aralığı 1,176-2,677), paritenin (%95 güven aralığı 1,138-2,033) ve gebelik haftalarının (%95 güven aralığı 1,003-1,006) doğum sonrası anemi şiddetinin bağımsız risk faktörleri olduğunu ortaya çıkarmıştır.

Sonuç: Gebelik anemisi sezaryen doğum oranlarını artırmakta ve vajinal doğum oranlarını azaltmaktadır. Gravidite, parite ve gebelik yaşı, yaş ve VKİ'den bağımsız olarak aneminin şiddetini artırır. Anemik gebe kadınların demir takviyesi ile tedavi edilmesi, sezaryen oranlarını azaltabilir ve normal doğum oranlarını daha uygun maliyetli bir şekilde artırabilir.

Anahtar kelimeler: Demir eksikliği anemisi, feto-maternal morbidite, maliyet etkinliği, üçüncü trimester

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Introduction

Anemia occurs when hemoglobin (Hb) is below the values determined by age and gender (1). The World Health Organization (WHO) defined anemia as a Hb concentration below 12 g/dL in women and 13 g/dL in men (2,3). Anemia is characterized by decreased oxygen-carrying capacity of erythrocytes to tissues. Decreased tissue oxygenation is reflected in patients with delay or difficulty in performing the functions of the cells. Although anemia can be seen in all age groups, children, pregnant women, and the elderly are the most affected. Although it varies from country to country, anemia is observed in approximately 38% of all pregnant women (4-6). The prevalence of anemia in pregnancy in industrial societies is one third of the developing countries (6,7). Anemia in pregnant women presents a spectrum ranging from simple clinical symptoms to preterm labor and maternal or fetal death. Newborns of untreated anemic pregnant women are often born with low birth weight. An increase in maternal morbidity and mortality occurs in proportion to the amount of blood lost by anemic pregnant women during vaginal delivery or cesarean section (8). The increase in plasma volume due to physiological changes during pregnancy intensifies anemia dilutionally. Therefore, patients experience clinical symptoms due to a decrease in oxygen capacity from the second trimester.

Apart from previous studies, there are no comprehensive data on the prevalence of anemia in pregnant women in Turkey. Turkey is in the category of developing countries, and the prevalence of pregnancy anemia is quite high, and this incidence decreases or increases according to geographical regions. In addition, because the diagnosis of anemia is made according to the Hb values in different trimesters, it is difficult to comment on the true prevalence of anemia in pregnancy. It is possible to encounter pregnancy anemia in roughly 28-40% of all pregnant women (9-11). This study was planned to investigate the effects of demographic parameters such as age, parity, and body mass index (BMI) on the prevalence of anemia, fetomaternal, and adverse pregnancy outcomes in pregnancy.

Materials and Methods

This retrospective study was initiated after the University of Health Sciences Turkey, İstanbul Training and Research Hospital Ethics Committee decided that it was ethically appropriate with the decision dated 07.07.2010 and numbered 2/19. In the review of medical records, pregnant women in the third trimester with an Hb value of <11 g/dL were included in the study. The Declaration of Helsinki was followed throughout the study. A total of 240 third trimester patients whose Hb values were compatible with anemia who applied to the Pregnancy Polyclinic of the University of Health Sciences Turkey, İstanbul Training and Research Hospital, Department of Obstetrics and Gynecology between 2015 and 2022 were selected as the study group. Two hundred forty healthy pregnant women without anemia were taken as the control group. In the third trimester, blood samples were taken at least twice for the diagnosis of anemia. According to the WHO, if the Hb value was <11 g/dL in any trimester, anemia was diagnosed, so patients below this value were considered to have anemia during pregnancy. Patients diagnosed with anemia in the first or second trimester were excluded from the study because they were given iron replacement. Between 28-42 weeks of gestation were considered as the third trimester. Multiple pregnancies, pregnant women who received iron replacement therapy in the first trimester, those having gestational diabetes, hypertension, systemic diseases and fetal anomalies were not included in the study.

Term singleton pregnant women between the ages of 18 and 40 years without systemic diseases, multiple pregnancies, placental adhesion anomalies, or Hb synthesis diseases were included in the study. Patient data were retrospectively scanned from medial records. Those over the age of 40 years, those who had blood transfusion in the last 3 months, and those with hematological disease who had multiple pregnancy detected on ultrasonography were excluded from the study.

Fetomaternal outcome, delivery types, hypertension, gestational diabetes, preeclampsia, ablatio placentae, polyhydramnios or oligohydramnios, premature rupture of membranes, preterm delivery, fetal birth weight, and intensive care unit rates were recorded. Gestational age at birth was defined by routine ultrasound scanning in the first trimester (between 0-13+6 weeks of gestation) (12,13). Anemia was diagnosed according to the WHO criteria, and participants were divided into mild, moderate, and severe (3). Table 1 shows the anemia groups according to Hb values. If the fetal weight was 4000 g or more, macrosomia was diagnosed. Fetal weight <2500 g was considered as low birth weight. Patients who gave birth before 37 weeks of gestation were defined as having a premature birth. Gestational diabetus (GDM) was diagnosed with 50 g and 75 g OGCT performed between 24 and 28 weeks. The diagnosis of hypertensive diseases was made by clinical evaluation, blood, and urinalysis.

Statistical Analysis

The number of participants was determined by power analysis using G*Power version 3.1.9.4. Cohen's d effect size was 0.80; α value 0.05; the power (1-β) value was taken as 0.80, and the number of samples required for one-tailed statistical comparison of anemic and non-anemic groups was calculated as n=240 for each group (12). Data were analyzed using the SPSS version 22.0 statistical package program (Statistical Package for Social Sciences, version 22.0, SPSS Inc, Chicago, III, USA). Shapiro-Wilk test was used to determine the data distribution pattern. Variables with normal distribution were analyzed by independent sample t-test, and non-normal variables were analyzed with Mann-Whitney U test or Kruskal-Wallis test depending on the number of groups. Multivariate logistic regression analysis was performed to identify independent risk factors for anemia after adjusting for age and BMI. Data are given as mean ± standard deviation for continuous variables and as frequency (percentage) for categorical variables. Two-tailed p-values of $p<0.05$ were considered significant.

Results

According to the WHO classification of anemia, the number of patients with mild anemia (53.3%) was significantly higher than that of patients with moderate (30%) and severe anemia (16.6%) (Table 1). As can be clearly seen in Table 2, no significant difference was found between the demographic characteristics of the anemic and non-anemic groups. When the perinatal outcomes of the groups were compared, cesarean section rates were found to be significantly higher in the anemic group than in the non-anemic group. There was no significant difference between the groups in terms of vaginal delivery rates. Oligohydramnsiosis and GDM rates were similar in both groups. The premature birth rate was higher in the anemic group. Ablatio placenta and preterm prematüre rupture of membrane (PPROM) were higher in anemic patients. The rate of low birth weight was higher in newborns in the anemic group. Fetal distress and neonatal intensive care unit were higher in anemic pregnant women (Table 3). Multivariate logistic regression analysis revealed that high gravidity (95% confidence interval 1.176-2.677), parity (95% confidence interval 1.138-2.033), and gestational weeks (95% confidence interval 1.003-1.006), were independent risk factors for anemia severity after adjustment for potential confounders, including age and BMI (Table 4).

Discussion

Iron deficiency anemia continues to be an important public health problem in obstetric practice because of the decrease in normal birth rates and the increase in costs associated with cesarean delivery. Our study was designed to analyze the morbidities observed in patients diagnosed with third trimester anemia and their newborns. Independent variables contributing to anemia severity were also determined by multivariate analysis. Because iron replacement was performed in these patients, our results cannot be compared with those of the control group. Because iron deficiency was determined according to WHO criteria and classified as mild, moderate, or severe, it was

Table 1. Anemia groups according to the Hb values

	Mild	Moderate	Severe	
Hemoglobin values	100-109 g/L	70-79 g/L	<70 g/L	
*Anemic group (n=240)	128 (53.3%)	72 (30%)	40 (16.6%)	Results are given as numbers (%)
*Non-anemic group (n=240)	Hb values were within physiological limits.			

*WHO (World Health Organization) hemoglobin concentrations for the diagnosis of anemia and assessment of severity. Edited by the World Health Organization, 2011. Hb: Hemoglobin

Table 2. Demographic characteristics of anemic and non-anemic pregnant women

	Pregnant women with anemia	Non-anemic pregnant women	p-values
N	240 (50%)	240 (50%)	
Age	28.0±4.02 (27-30)	28.8±3.09 (26-32)	0.08
Gravidity	2.05±0.11 (1-3)	1.98±0.02 (1-3)	0.50
Parity	1.20±0.20 (1-1.4)	0.98±0.03(0-1)	0.34
BMI	22.0±405	22.8±3.06	0.20
Gestational week	28.4±4.11	29.2±4.30	0.45

BMI: Body mass index, results are given in means ± standard deviation or n (%). P-values of >0.05 were considered insignificant

Table 3. Perinatal and maternal morbidities in anemic and healthy pregnant women

	Anemic (240)	Non-anemic (240)	p-values
C/S	170 (70.8%)	120 (50%)	**0.01**
Vaginal birth	70 (29.2%)	120 (50%)	**0.01**
Oligohydramnios	48 (20.8%)	48 (20%)	0.56
Preterm birth	36 (15%)	24 (10%)	**0.04**
GDM	24 (10%)	24 (10%)	0.30
Hypertensive disorders	22 (9.1%)	28 (11.6%)	0.43
Abruptio placenta	6 (2.5%)	0 (0%)	**0.01**
PPROM	12 (5%)	8 (3.3%)	**0.02**
Low birth weight (<2500 g)	20 (8.3%)	15.8 (6.6)	**0.03**
Fetal distress	46 (19.1%)	36 (15%)	**0.01**
NICU admission	24 (10%)	16 (6.6%)	**0.02**

C/S: Ceserean section, GDM: Gestational diabetes mellitus, PPROM: Preterm premature rupture of membrane, results are given in numbers (%). A p-value of <0.05 was considered significant for all bold values, NICU: Neonatal intensive care unit

Table 4. Logistic regression analysis of the effects of gravididy, parity, and gestational weeks on anemia severity after adjustment for age and BMI

	Unadjusted		Adjusted (1)	
	OR (95% CI)	p	OR (95% CI)	p
Gravidity	1.151 (1.132-2.216)	**<0.001**	1.738 (1.176-2.677)	**<0.01**
Parity	1.518 (1.122-2.232)	**<0.01**	1.324 (1.138-2.033)	**<0.05**
Gestational weeks	1.003 (1.001-1.008)	**<0.01**	1.004 (1.003-1.006)	**<0.05**

OR: Odds ratio, CI: Confidence interval, BMI: Body mass index, a p-value of <0.05 was considered significant for all bold values

possible to compare the relationship between anemia severity and perinatal and maternal outcomes (12).

Iron deficiency remains an important public health problem in developing countries. It is possible to encounter anemia in different prevalences in every society according to geography, culture, economy, and education level. The decrease in daytime performance due to the decrease in the oxygen carrying capacity of the patient causes early fatigue and activity restriction. The co-existence of pregnancy and anemia causes worsening of the clinical picture. Fetal development is affected at different stages, as maternal iron stores will be depleted due to the increased need for iron during gestational weeks. Sometimes, lack of amniotic fluid and hypertensive changes due to vascular bed damage cause worsening of the clinical picture. An increase in cesarean delivery rates due to fetal distress. Owing to all these negative effects, anemic pregnant women are more prone to morbidity than healthy controls in terms of both maternal and fetal outcomes (9-11). In a study by Breymann (14) it was determined that maternal anemia may have both maternal and fetal effects, and it was shown that enzymatic functions, mental functions, muscle and cardiac effects on the mother may occur, and these effects indirectly affect the fetus. Fetally, it has been reported that there are risks of fetal tension retardation, preterm birth, and may even be associated with a developing preeclampsia (14).

The prevalence of iron deficiency anemia has decreased in the last two decades in our country. Close monitoring of pregnant women in terms of anemia in health centers has become a state policy. Providing the necessary drugs for iron replacement free of charge to patients with iron deficiency and strict controls after treatment played an important role in reducing the incidence of the disease. For all these reasons, while the prevalence of anemia in our country used to be quite below the European average, it has now approached the developed country averages over the years. However, it still continues to be an important public health problem in our country, especially in the pregnant population (15,16). Despite all these advances in diagnosis and treatment, pregnancy anemia continues to increase both fetal and maternal morbidity. The prevalence of anemia-related PPROM and placental diseases continues to increase. Because these obstetric problems increase the cesarean section rates, morbidities such as bleeding and infection are still increasing. The intensive care needs of bloodless mothers are considerably higher than those of

healthy newborns. This increases both neonatal morbidity and the cost (9,11).

The fact that gestational anemia plays a critical role in determining the mode of birth requires that this public health problem be treated. In the current study, 170 patients (70.8%) in the anemic group underwent cesarean section, whereas this rate was 120 (50%) in the non-anemic group. Anemia has led to a 20% increase in cesarean delivery rates. When iron deficiency anemia in pregnancy is treated with conventional iron preparations, the rate of patients having a normal vaginal birth will be higher than that after cesarean delivery (17-20). Considering the cost of a cesarean birth to the hospital and the country, correcting anemia with iron supplementation would be a more cost-effective approach. Detecting anemic patients by conducting iron deficiency screening programs before or during pregnancy can be made a state policy. To reduce the rate of cesarean section due to anemia, it should be made easier for pregnant women to use iron preparations. Thus, the expenses that the patient and the social insurance institution will pay due to the cesarean section surgery and the duration of hospital stay should be minimized.

Conclusion

The acceptance of pregnancy anemia as an important disease by health professionals at all stages, starting from primary care physicians, will be an important step toward a solution. The foundations of a society rising thanks to healthy generations and mothers will be possible by treating this clinical picture in every region of our country. As the prevalence of anemia will decrease and normal birth rates will increase, the morbidity and costs associated with cesarean section will also decrease.

Ethics

Ethics Committee Approval: This retrospective study was initiated after the University of Health Sciences Turkey, İstanbul Training and Research Hospital Ethics Committee decided that it was ethically appropriate with the decision dated 07.07.2010 and numbered 2/19.

Informed Consent: Not necessary for this manuscript.

Authorship Contributions

Concept: R.Ö., E.B., Design: R.Ö., E.B., Data Collection or Processing: R.Ö., E.B., Analysis or Interpretation: R.Ö., E.B., Literature Search: R.Ö., E.B., Writing: R.Ö., E.B.

Conflict of Interest: No conflict of interest was declared by the authors.

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ORIGINAL RESEARCH

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Retrospective Evaluation of the Preoperative Features of Breast Cancer and Sentinel Lymph Node Metastasis

Meme Kanserinde Sentinel Lenf Nodu Metastazının Preoperatif Özelliklerinin Retrospektif Değerlendirilmesi

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Abstract

Objective: Determining the presence of metastasis in the axillary lymph nodes using preoperative data in breast cancer has been studied previously. Formulas and nomogram programs that calculate the relationship between parameters and axillary lymph node metastases are presented. It is controversial whether current calculations give the same accuracy across all ethnic groups. We aimed to validate the Memorial Sloan Kettering Cancer Center (MSKCC) nomogram results for the prediction of sentinel lymph node (SLN) metastasis in patients with breast cancer in Turkey.

Method: The clinical records, pathology results, and surgery reports of 400 patients who underwent surgery were examined. Sensitivity, specificity, positive and negative predicated values, and area under the curve (AUC) values were calculated using a nomogram developed by the MSKCC.

Results: Frozen section results of SLN examination of the patients were positive in 101 of the 400 patients. The relationship between nomogram calculation and sentinel positivity was evaluated using the receiver operating characteristic curve (ROC); AUC 0,699, p<0.001. When sentinel lymph node biopsy (SLNB) status and nomogram risk ratio were compared, the sensitivity was calculated as 85% and the specificity was 40%. The negative predicated value was 68% and the positive predicated value was 63%. The ROC curve calculation reached a risk value of 77% as the optimal criterion. When this value was reached, the nomogram's sensitivity was 96% and specificity was 14.8%.

Conclusion: Although there was a significant relationship in the calculation of MSKCC nomograms in our patient group, it was found to show an excessive risk of metastasis. Both sensitivity and specificity

Öz

Amaç: Meme kanserinde aksiller lenf nodu metastazı riskini hesaplayan formüller ve nomogram programları sunulmuştur. Mevcut hesaplamaların tüm etnik gruplarda aynı doğruluğu verip vermediği tartışmalıdır. Türkiye'deki meme kanserli hastalarda sentinel lenf nodu metastazı (SLNB) öngörüsünde Memorial Sloan Kettering Kanser Merkezi (MSKCC) nomogram sonuçlarını doğrulamak istedik.

Yöntem: Cerrahi kliniğimizde ameliyat edilen 400 hastanın klinik kayıtları, patoloji sonuçları ve ameliyat raporları incelendi. Duyarlılık, özgüllük, pozitif ve negatif öngörü değerleri ve eğri altındaki alan (AUC) değerleri MSKCC tarafından geliştirilen nomogram kullanılarak hesaplandı.

Bulgular: Hastaların SLN incelemesinin frozen kesit sonuçları 400 hastanın 101'inde pozitifti. Nomogram hesaplaması ile sentinel pozitifliği arasındaki ilişki, alıcı işletim karakteristik eğrisi (ROC) kullanılarak değerlendirildi; AUC 0,699, p<0,001. Sentinel lenf nodu biyopsisi (SLNB) durumu ile nomogram risk oranı karşılaştırıldığında duyarlılığı %85, özgüllüğü %40 olarak hesaplandı. Negatif yüklemli değer %68, pozitif yüklemli değer ise %63 oldu. ROC eğrisi hesaplaması optimal kriter olarak %77 risk değerine ulaştı. Bu değere ulaşıldığında nomogramın duyarlılığı %96, özgüllüğü ise %14,8 idi.

Sonuç: Hasta grubumuzda MSKCC nomogramlarının hesaplanmasında anlamlı ilişki olmasına rağmen aşırı metastaz riski gösterdiği tespit edildi. Özellikle optimal risk değerleri dikkate alındığında hem duyarlılık hem de özgüllük değerleri batılı çalışmalara göre anlamlı derecede düşük bulunmuştur. Sonuçlarımızın Avrupa ve Amerika popülasyonlarını temel alan çalışmalarla karşılaştırıldığında Asya popülasyonu üzerine yapılan çalışmalara daha benzer olduğu görüldü. Farklı etnik popülasyonların

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values were found to be significantly lower than those in western studies, especially when optimal risk values were considered. Our results were found to be more similar to the studies on the Asian population when compared with the studies based on European and American populations. It was concluded that different ethnic populations may have their own characteristics and that a nomogram calculation that is specifically designed for each ethnic population may be required.

Keywords: Breast cancer, breast surgery, nomogram, sentinel lymph node

kendine has özellikleri olabileceği ve her etnik popülasyona özel tasarlanmış bir nomogram hesaplamasının gerekli olabileceği sonucuna varılmıştır.

Anahtar kelimeler: Meme cerrahisi, meme kanseri, nomogram, sentinel lenf nodu

Introduction

Axillary lymph node metastasis is one of the most important prognostic factors in breast cancer patients. Primary breast cancer most often metastasizes to axillary lymph nodes (1,2). Ninety-five percent of women who die from breast cancer have axillary lymph node metastases, and the most important factor in determining prognostic factors and providing cures is the presence of metastases at the Axillary lymph nodes (3). While the risk of recurrent cancer in patients with axillary lymph node metastasis is above 75%, the same risk decreases to 30% in patients with non-metastatic axillary lymph nodes

Axillary lymph node dissection leads to high morbidity and is not necessary in every patient. For this reason, sentinel lymph node biopsy (SLNB) has been replaced with axial dissection in patients with early breast cancer because of its less invasive nature and highly accurate results (4-7).

The Memorial Sloan Kettering Cancer Center nomogram calculation is one of the most widely used international validation nomogram studies. In studies conducted on the American population, preoperative parameters of the patients were investigated and statistical formulas were created (8). In our study, the validity of this nomogram on the Turkish population was investigated.

Although the MSKCC nomogram was based on nine parameters, we also investigated possible connections by adding other parameters. In our study, age, tumor type, tumor size, palpability, tumor location, number of tumors, presence of necrosis, presence of ductal carcinoma *in situ* (DCIS) component, estrogen receptor (ER) -progesterone receptor (PR)- human epithelial growth factor 2 receptor (HER2) presence, Ki-67 index, lymphatic-neural invasion presence, grade of tumor data, and sentinel lymph node positivity were compared.

Materials and Methods

Clinical records, pathology results, and surgery reports of 400 patients with breast cancer who underwent surgery were examined. Female patients and those who underwent peroperative SLNB were included in the study. Patients with the following criteria were excluded from the study: Patients who received neoadjuvant chemotherapy treatment, patients with previous breast cancer history, and patients who underwent breast or axillary surgery previously. Before starting the incision, 5 cc of methylene blue (Blumet 100 mg/10 mL Vem pharmaceuticals İstanbul/Turkey) was injected in equal amounts at the 3, 6, 9, and 12 o'clock dials on the edge of the areola. The SLNB procedure was performed within the next 5 min. Fallowing the axillary incision, the axillary lounge reached and sentinel lymph nodes, which were stained with methylene blue, were longitudinally directed and submitted to the frozen section evaluation. The pathologist (Ç.V.), stained the specimens with hematoxylin and eosin and examined for metastases. SLN metastases were classified as macrometastasis for diameter ≥2 mm, micrometastasis for diameter 2 mm, and isolated tumor cells for clusters that did not meet the micrometastasis criteria and were 2 mm in diameter. Patients with macrometastasis underwent ALND.

All patients underwent surgery using the same surgical procedures, either conservative surgery or total mastectomy. For non-palpable breast lesions, a guided wire was used.

This study was approved by the Ethics Committee of Kocaeli University Faculty of Medicine on 18.06.2020 with number 212 (KÜ GOKAEK 2020/212). This study was conducted in accordance with the Declaration of Helsinki.

Statistical Analysis

Calculations were made using a nomogram that is available on the MSKCC website (http://nomograms.mskcc.org/breast/BreastSLNodeMetastasisPage.aspx) (age, tumor size, tumor type, tumor placement-upper inner quadrant, lymphatic-neural invasion presence, multifocality, tumor type and grade, ER and PR presence). In addition, palpability, necrosis presence, DCIS component presence, HER2 receptor presence, and Ki-67 index were determined and their relationship with sentinel lymph nodule positivity was

evaluated. Non-nomogram parameters did not participate in sensitivity, speciality, positive and negative predicated values, or receiver operating characteristic (ROC)- area under the curve (AUC) calculation.

Statistical evaluation was performed using the IBM SPSS 20.0 (IBM Corp., Armonk, NY, USA) package program. The normal dispersion conformity test was evaluated using the Kolmogorov-Smirnov test. Numerical variables are given as median (25^{th}-75^{th} percentile) and frequency (percentages). For numerical variables that did not have normal distribution, Fisher's Exact, Yeates' kikar test, Pearson's chi-squared, and Monte Carlo's chi-squared tests were used in categorical variables with the Mann-Whitney U test. ROC analysis was used in sentinel metastasis groups to determine sensitivity, specificity, and cut-off points of nomogram values. The optimal cut-off value was determined using ROC analysis and AUC values. $p<0.05$ was considered sufficient for statistical significance in two-way tests.

Results

Four hundred patients were included in the study after removing those who did not meet the criteria. When the demographic characteristics of the patients who participated in the study were examined, the mean age was evaluated as 55 (Table 1). Invasive ductal breast cancer was found in 77% of the patients (308 of 400). In 61% of the patients (244 of 400 patients), the tumor was 2 cm, and 1.5% (in 6 of 400 patients) of the patients had a mass >5 cm (Table 1). In 64.5% of patients (258 of 400), the tumor was palpable on preoperative examination (Table 1). In 64.3% of the patients, the tumor was on the upper outer quadrant (Table 1). In 89.3% (357 of 400) of the patients, a single mass and multiple lesions were detected in the remaining patients (43 of 400). The necrosis component was present in 17.2% of patients (69 of 400) (Table 1). The DCIS component accompanying the tumor was observed in 61% (244 of 400) of the patients. ER positive was observed in 82.8% (331 of 400) of patients and PR positive in 77.5% (310 of 400). HER2 was positive in 30% (120 of 400) of patients. In 77.5% (310 of 400) of the patients, the Ki-67 index was above 30%, and a significant association was found with sentinel lymph node positivity (Table 1). Tumor grades in patients were detected as garde 1 in 27.3%, grade 2 in 47.8%, and grade 3 in 25%. Lymphatic invasion was found in 26% (144 of 400) of patients, and a significant association was found with sentinel lymph node positivity (Table 1). Neural invasion was observed in 18.8% (75 of 400) of the patients, and a significant association was found with sentinel lymph node positivity (Table 1).

In 101 of the 400 patients (25.25%), the sentinel lymph nodes were positive. The relationship between nomogram percentage and sentinel lymph node positivity was

Table 1. Demographic features of patients included in the study

Variable		SLNB -	SLNB +
Age	≤30	6	2
	31-40	35	13
	41-50	77	27
	51-60	82	26
	61-70	63	15
	71+	36	18
Tumor size	≤2 cm	193	52
	2-5 cm	102	7
	>5 cm	4	2
Palpabilite	Yes	189	69
	No	37	5
Tumor location	UOQ	187	70
	UIQ	28	5
	IOQ	46	11
	IIQ	27	11
	Central	11	4
Multifocality	Yes	32	11
	No	67	90
Operation	Lumpectomy	247	71
	Mastectomy	52	30
Histotype	Ductal	291	98
	Lobular	6	3
	Other	2	0
Grade	Low (1-2)	230	70
	High (3)	69	31
ER	+	242	89
	-	57	12
PR	+	223	87
	-	76	14
HER2	+	94	26
	-	205	75
Lymphovascular invasion	+	89	55
	-	210	46
Necrosis component	+	40	29
	-	259	72
DCIS component	+	175	69
	-	124	32
Ki-67 index	High	223	87
	Low	76	14
Neural invasion	+	45	30
	-	254	71

SLNB: Sentinel lymph node biopsy, ER: Estrogen receptor, PR: Progesterone receptor, HER2: Human epidermal growth factor 2, DCIS: Ductal carcinoma *in situ*

evaluated using the ROC curve. AUC 0.699 was found to be p<0.001 (Table 2, Figure 1). A risk ratio of 77% or more was calculated in the nomogram as the optimal criterion (Table 2). When the SLNB status and nomogram risk ratio were compared, the sensitivity was calculated as 85% and the specificity was 40%. The negative predicated value was calculated as 68% and the positive predicated value was 63%. The ROC curve calculation reached a risk value of 77% as the optimal criterion. When this value was reached, the nomogram's sensitivity was 96% and its specificity was 14.8%.

Table 2. ROC of the study

ROC curve	
Variable	Nomogram
Classification variable	Sentinel lymph node metastasis
Number of instances	400
SLNB positive group	101 (25.25%)
SLNB negative group	299 (74.75%)
Prevalence of disease (%)	25.3
Area under the ROC curve (AUC)	0.699
Standard error	0.0285
95% confidence interval	0.652 to 0.744
95% bootstrap CI	0.646 to 0.751
Z statistic	7.001
Significance level p (area=0.5)	<0.0001
Optimal criterion	0.77
95% safe interval	>0.728668183 to >0.89

SLNB: Sentinel lymph node biopsy, ROC: Receiver operating characteristic, CI: Confidence interval, AUC: Area under the curve

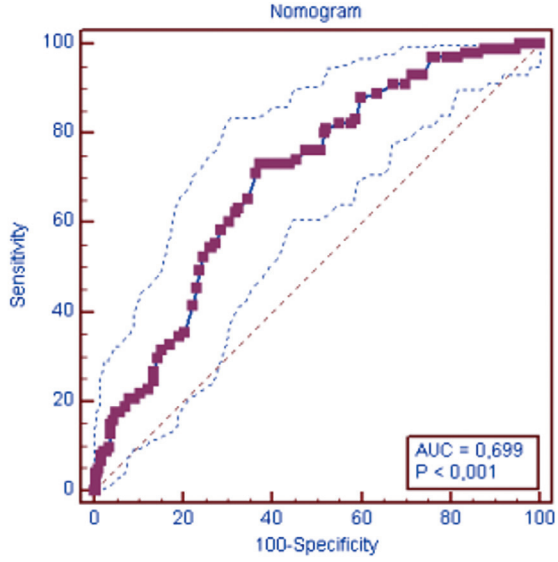

Figure 1. Area under the curve (AUC) graphics of the study

Discussion

Detecting metastasis in the axillary lymph nodes in patients with breast cancer during preoperative evaluation has been the subject of many studies. It is controversial whether current calculations give the same accuracy across all ethnic groups, and according to our knowledge, no nomogram calculation specific to the Turkish population exists. The MSKCC nomogram calculation is one of the most used international validation nomograms (8). In our study, the validity of this nomogram on the Turkish population was investigated. From the parameters that we have added within the nomogram; necrosis component, high Ki-67 index, and lymphatic and neural invasion were found to be directly related to sentinel lymph node positivity. When looking at the average age, most patients were approximately 41-50 and 51-60 years old, while the median value was calculated as 55. The current data showed that the age range most commonly seen with breast cancer was similar to national cancer data from China, Japan, and America (9,10). Because of the study, the ROC curve value was calculated as 0.699. Considering that 0.5 is a 50% chance and 1 result is a definitive diagnosis, the result of the study gives a meaningful estimate value but casts doubt on its validity in our population.

From similar studies, Vieni et al. (11) used the MSKCC nomogram in 175 patients in Palermo; When AUC value was calculated as 0.885% and the cut-off value was calculated as 50%, 81.4% specificity, 92.3% sensitivity, 80% positive predicated, and 92.9% negative predicated values were calculated. In the study of Qiu et al. (12), 1227 patients in Shunung in the People's Republic of China, the AUC calculated the value as 0.73. At their optimal criterion ratio of 70%, a predicated rate of 96% was found. Although the results were not exactly the same, they were found to have more similar characteristics to those performed in the Asian population.

Ki-67 proliferation index is often associated with poor prognosis in patients with breast cancer. In the study of Chung et al. (13), 367 patients from Seoul found a relationship between the Ki-67 proliferation index and SLN metastasis (p=0.038). Similar to similar studies in the literature, our study found an increased risk of axillary metastasis in patients with a high Ki-67 index (13,14). However, studies that have not found a link between the Ki-67 proliferation index and SLN metastasis are also present in the literature, including the study of the Milan group of 4351 patients (15).

Nomogram gave high sensitivity results in our patient group but showed low specificity values, as opposed to European research. Sentinel lymph node metastasis risk has been shown in similar studies of tumors with lymphovascular invasion. In a study of 4.351 patients in Milan, Viale et al. (15) evaluated lymphovascular insulation as the strongest independent parameter in sentinel lymph node metastasis. The lymphosvascular invasion relationship has been reported in studies both in our country and in Canada. These studies include those of Ozmen et al. (16) in 400 patients in İstanbul and 3786 patients at MSKCC NY. In our study, SLNB positivity increased significantly in patients with lymphovascular invasion (13-18).

A limited number of studies have investigated the link between tumor necrosis and axillary lymph node metastasis. In a study following DCIS cases with microinvasion, no association was found between comedo necrosis and axillary lymph node metastasis (19). In our study, lymphatic invasion (26%) and neural invasion (18.8%), Ki-67 index elevation (77.5%) and necrosis presence (17.2%) were found to be associated with SLN positivity.

Perineural invasion has been frequently associated with lymphatic tumor emboli in high-grade tumors. In our study, we frequently monitored lymphovascular invasion in patients with perineural invasion (20).

In patients with breast cancer; age, ER, PR, HER2 conditions, and race affect prognosis. While the triple-negative phenotype was predominant in African-American breast cancer patients, most cases in Asian countries were ER- and PR-negative and HER2-positive (21). In our study, it was found that most of the cases were ER and PR positive.

The surgical dissection techniques are also shown to make significant differences between the published articles. In our center, all blue-stained SLNs were dissected; however, in some centers, reaching a certain number of SLNs is considered sufficient. As a result, the number of SLNs dissected and excised may change the nomogram accuracy because increasing the number of non-SLNs involved may correspond to fewer SLNs being removed (22).

Study Limitations

In this study, SLNB was performed using methylene blue alone. Despite the limitations of the study, it is available in the literature that methylene blue alone is a safe, cost-effective, and successful method in the progression of sentinel lymph node metastasis of breast cancer (23,24).

Conclusion

Although there was a significant relationship in the calculation of MSKCC nomograms in our patient group, it was found to show an excessive risk. Similar studies found that different results were calculated for different races. Our results were found to be more similar to studies on the Asian population compared to studies based on European and American populations. It was concluded that different ethnic populations may have their own characteristics and that a nomogram calculation that is specifically designed for each ethnic population may be required. Parameters apart from the current nomogram values might be meaningful for these populations. Prospective studies on this subject should be planned in different centers across the country, and the meaningful results that we found should be strengthened.

Ethics

Ethics Committee Approval: This study was approved by the Ethics Committee of Kocaeli University Faculty of Medicine on 18.06.2020 with number 212 (KÜ GOKAEK 2020/212). This study was conducted in accordance with the Declaration of Helsinki.

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: A.K., N.Z.C., N.Z.U., Concept: A.K., K.K., N.Z.U., Design: A.K., K.K., Data Collection or Processing: A.K., N.Z.C., N.Z.U., Analysis or Interpretation: A.K., N.Z.C., N.Z.U., Literature Search: A.K., K.K., N.Z.U., Writing: A.K., K.K.

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ORIGINAL RESEARCH

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Impact of Pfizer-BioNTech COVID-19 Vaccination on the Menstrual Cycle

Pfizer-BioNTech COVID-19 Aşısının Menstrüel Döngü Üzerindeki Etkisi

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Abstract

Objective: To evaluate the effect of Pfizer-BioNTech Coronavirus disease-2019 (COVID-19) vaccination on the menstrual cycle.

Method: This cross-sectional survey study investigated whether Pfizer-BioNTech COVID-19 vaccination affected the menstrual cycle of women who had regular cycles.

Results: One hundred and sixty two of 327 (49.5%) patients who had regular cycles expressed that their menstrual cycle had been affected after vaccination. Univariate analysis revealed a statistically significant relationship between age, body mass index (BMI), parity, smoking, pads per day, intrauterin device (IUD) and the incidence of menstrual change after vaccination. The factors identified by multivariate analysis as being independently related with the menstrual disorders following vaccination were BMI [odds ratio (OR) 1.09, 95% confidence interval (CI) 1.01-1.17, p=0.023], smoking (OR 2.19, 95% CI 1.28-3.78, p=0.005), pads per day (OR 1.42, 95% CI 1.14-1.75, p=0.005) and IUD (OR 5.1, 95% CI 1.99- 13.0, p=0.001).

Conclusion: Approximately half of the participants declared menstrual disorder after vaccination. BMI, smoking, number of pads per day, and IUD were found to be independent risk factors for menstrual changes.

Keywords: COVID-19, menstrual cycle, Pfizer-BioNTech, vaccination

Öz

Amaç: Pfizer-BioNTech Koronavirüs hastalığı-2019 (COVID-19) aşısının menstrüel döngü üzerindeki etkisini değerlendirmektir.

Yöntem: Bu anket çalışması ile, Pfizer-BioNTech COVID-19 aşısının düzenli menstrüel siklusu olan kadınların menstrüel döngüsünü etkileyip etkilemediğini araştırılmıştır.

Bulgular: Menstrüel siklusu düzenli olan 327 kadından 162'si (%49,5), menstrüel döngüsünün aşılamadan sonra etkilendiğini belirtmiştir. Univaryant analiz sonucunda aşılama sonrası adet değişim insidansı ile yaş, vücut kitle indeksi (VKİ), parite, sigara, günlük ped sayısı, rahim içi araç (RİA) arasında istatistiksel olarak anlamlı bir ilişki olduğu ortaya konulmuştur. Multivaryant sonucunda ise bağımsız olarak ilişkili olarak tanımlanan faktörler VKİ [olasılık oranı (OO) 1,09, %95 güven aralığı (GA) 1,01-1,17, p=0,023], sigara (OO 2,19, %95 GA 1,28-3,78, p=0,005), günlük ped sayısı (OO 1,42, %95 GA 1,14-1,75, p=0,005) ve RİA (OO 5,1, %95 GA 1,99-13,0, p=0,001) olarak bulunmuştur.

Sonuç: Çalışmaya katılan kadınların yaklaşık yarısı aşı sonrası adet düzensizliği bildirmiştir. VKİ, sigara, günlük ped sayısı ve RİA adet düzensizliği için bağımsız risk faktörü olarak bulunmuştur.

Anahtar kelimeler: Aşı, COVID-19, menstrüasyon, Pfizer-BioNTech

Introduction

In Turkey, the first Coronavirus disease-2019 (COVID-19) case was identified in March 2020, and the first doses of the Pfizer-BioNTech COVID-19 vaccine were administered in July 2021(1). Previously published studies reported that major and minor menstrual disorders were observed after administration of the Pfizer-BioNTech COVID-19 vaccine (2). Menstrual irregularities, such as heavy bleeding, and shorter or longer cycles have been described in numerous reports of recent research evaluating menstrual disorders connected to severe acute respiratory syndrome-coronavirus-2 immunization (3,4). In the same sense that irregular menstruation can raise concerns about fertility in women of childbearing age, postmenopausal bleeding

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can raise fears about endometrial cancer. For this purpose, we designed this study to determine whether the vaccine affected menstrual cycles.

Materials and Methods

This study was approved by Ethics Committee of University of Health Sciences Turkey, Derince Training and Research Hospital, Non-Invasive Clinic Ethics Committee (approval date 27.10.22, institution review board number: 2022-92), patients who received the Pfizer-BioNTech COVID-19 vaccine were informed and included in the study if they gave consent. They were asked to complete a survey form created via Google or face-to-face. Information was given about the study's voluntary nature, which stated that the findings would not be disclosed to any outside parties. The questionnaire asked about the individuals' demographics and menstrual patterns (period time, pads per day, pain) of premenopausal patients before and after vaccination (Supplementery File 1). The vaccination had been administered at least 3 months prior to the survey. Patients were asked to provide details about their menstrual cycle following any dose of the Pfizer-BioNTech COVID-19 vaccine. It was also questioned whether postmenopausal patients had bleeding.

Healthy women over the age of 18 years with regular menstrual cycles and without a previous history of abnormal bleeding were included in the study. Patients who were of reproductive age were included if they had at least three cycles of post-pregnancy or post-hormonal contraceptive use.

Exclusion criteria included those with gynecological or hematological illnesses and those using oral contraceptives or the levonorgestrel-releasing intrauterine system (Mirena®).

At first, postmenopausal women were also asked to participate in the survey; however, as none of the participants reported breakthrough bleeding, this group was not included in the analysis of women of reproductive age to prevent misinterpretation.

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS) version 21.0 was used for all statistical analyses. Comparison of categorical variables was performed using exact Fisher's test, Pearson's chi-square test, and Yates continuity correction. After the normality of variables was examined by the Kolmogorov-Smirnov test, comparison of continuous variables was performed using an independent-samples t-test or Mann-Whitney U test. P-values <0.05 were considered statistically significant. Data are expressed as mean ± standard deviation or median and interquartile range for continuous variables, and absolute numbers and percentages for categorical values. Multivariate logistic regression was performed for variables that were significant in the univariate analysis. The odds ratio (OR) was supported by confidence intervals and p-values.

Results

Throughout the study, 392 questionnaires were completed. Four were excluded because of incomplete answers, 13 of them used oral contraceptive drugs, and 6 of them stated that they did not have regular periods. Twenty-three responders in all were excluded from the research, and with 369 participants overall, the study was finished. Forty-two of them were in the postmenopausal period. None of the postmenopausal women had postmenopausal bleeding following vaccination. The mean age of postmenopausal women was 56.3±7.2 years (range 45-68).

Excluding the postmenopausal group, 327 women of reproductive age were evaluated for statistical analysis. The mean age was 36.3±7.8 years (range 18-49). One hundred sixty-five of 327 women (51.5%) reported no change after being vaccinated. One hundred sixty-two (49.5%) women who had regular cycles stated that their menstrual cycle had been affected after vaccination. Sixty-nine women had unusually heavy flows after vaccination, and 75 had longer bleeding. Fourty-eight of these group of women both experienced heavy and longer bleeding. Eighteen women experienced breakthrough bleeding. Fifty-seven women had decreased menstrual bleeding, 33 had a shorter menstrual bleeding, and 21 of these experienced both decreased and shortened bleeding. Eighteen (5.5%) women expressed that they had menstrual cycles in longer time intervals, while 6 (1.8%) women had menstrual cycles more often. Dysmenorrhea developed in 15 of 178 patients (8.4%) who had not previously complained of dysmenorrhea.

There were no differences in the reported onset of new menstrual-related symptoms among patients who received one, two, three, or four vaccination doses (p=0.096). It was not associated with previous COVID-19 disease (p=0.493).

Univariate analysis revealed a statistically significant relationship between age, body mass index (BMI), parity, smoking, pads per day, intrauterine device use, and the incidence of menstrual change after vaccination (Table 1). It was found that the age of those who had menstrual

changes was older than that of those who did not (37.8±7.4 vs. 34.7±7.9, p<0.001) but it was not found statistically significantly by multivariate analysis (p=0.187). The factors identified by multivariate analysis as being independently related with the menstrual disorders following vaccination were BMI [OR 1.09, 95% confidence interval (CI) 1.01-1.17, p=0.023], smoking (OR 2.19, 95% CI 1.28-3.78, p=0.005), pads per day (OR 1.42, 95% CI 1.14-1.75, p=0.005) and intrauterin device (OR 5.1, 95% CI 1.99-13.0, p=0.001) (Table 2).

There was no statistically significant difference in age between the group that experienced an increase in bleeding and the group that experienced a decrease (39.2±5.6 vs. 37.5±8.6, p=0.217).

Of the 162 patients with menstrual disorders, 45 (27.8%) contacted a doctor, no issues found in 36 of them. Ovarian cysts were detected in 3 patients and premenopausal signs were found in 6 patients.

Discussion

Menstruation is an inflammatory process. Natural killer cells, macrophages, mast cells, neutrophils, dendritic cells, and T-cells are all drawn in throughout the menstrual cycle and contribute to the destruction and regeneration of the functional endometrium. The vaccination-induced systemic immune response may affect this inflammation (5). In addition, immune thrombocytopenia, in which both thrombotic and hemorrhagic events are observed following vaccination, is thought to occur via a heparin-induced thrombocytopenia-like mechanism (6,7). Menstrual alterations may be explained by immune-related procoagulative and pro-inflammatory states. Consistent with this, the recent research involving healthy participants found a link between receiving the COVID-19 vaccination and alterations in menstrual flow (3,8,9).

According to a web-based survey, 42% of people with regular menstrual cycles bled more heavily than usual, while 44% reported no change after being vaccinated. In addition,

Table 1. Characteristics of patients

	No change (n=165)	Change (n=162)	p
Age, y	34.7±7.9	37.8±7.4	<0.001
Parity	1 (0-2)	2 (0-2)	0.004
BMI, kg/m^2	23.3±3.7	24.7±3.6	<0.001
Smoking, n (%)	36 (21.8)	66 (40.7)	<0.001
Period time, day	5.8±1.4	6±1.3	0.084
Pads per day	2.6±1.0	3±1.1	0.001
Intrauterin device, n (%)	6 (3.6)	33 (20.4)	<0.001
COVID-19 disease history	36 (21.8)	30 (18.5)	0.493
Hypertension, n (%)	3 (1.8)	0 (0)	0.248
Diabetes mellitus, n (%)	3 (1.8)	6 (3.7)	0.333
Hypothyroidism, n (%)	6 (3.6)	3 (1.9)	0.502
Number of dosage, n (%)			0.096
One	24 (14.5)	33 (20.4)	
Two	75 (45.5)	81 (50)	
Three	60 (36.4)	39 (24.1)	
Four	6 (3.6)	9 (5.6)	

BMI: Body mass index, COVID-19: Coronavirus disease-2019

Table 2. Characteristic features of participants associated with post-vaccination menstrual irregularities

	OR	95% CI	p
Age	1.03	0.99-1.07	0.187
BMI	1.09	1.01-1.17	0.023
Parity	1.03	0.83-1.28	0.813
Smoking	2.19	1.28-3.78	0.005
Pre-vaccination used pads per day	1.38	1.10-1.72	0.005
Intrauterin device	5.1	1.99-13.0	0.001

Multivariate analysis was performed, OR: Odds ratio, CI: Confidence interval, BMI: Body mass index

66% of postmenopausal people reported breakthrough bleeding. They discovered a strong correlation between age and increased/breakthrough bleeding (3).

Up to 66% of the participants in another study reported experiencing new or worsening menstrual-related symptoms in the first cycle following vaccination; these changes were noted to be temporary after 2 months (10).

In the current study, various menstrual changes were observed. In addition to the observation of heavy and prolonged bleeding, the number of people reporting decreased and infrequent menstrual patterns was also significant. However, no patient experienced postmenopausal bleeding.

COVID-19-infected women experienced temporary menstrual abnormalities, primarily longer periods and decreased volume, as well as shortened or disordered menstrual cycles and increased volume, in line with vaccinated women (11,12). It was not the purpose of our study to investigate menstrual changes following COVID-19 disease. However, no relationship was found between history of COVID-19 disease and menstrual irregularities observed among vaccinated women.

In the current study, although the high ratio of being affected by the vaccine (n=162, 49.5%), the low rate (n=45, 27.8%) of consulting a doctor actually suggests that the complaints were either vague or temporary.

Study Limitations

The study's limitations include its small sample size, the subjectivity of the responses because there is variation in women's normal periods, and the possibility that participants' preconceived notions about the vaccine due to misinformation and anti-vaccine activists' discourse may influence the answers. Myths of vaccines regarding fertility and reproduction are especially powerful because they afflict a huge portion of the population.

It is important to show whether these changes can be linked to vaccination itself, clarify the duration of such changes, and begin to understand the mechanism of these vaccine-related menstrual changes. Therefore, it is necessary to quantify the prevalence of menstrual changes after vaccination in comparison with women vaccinated against other COVID-19 vaccines or unvaccinated control groups. By providing a more comprehensive understanding and open communication about potential menstrual changes related to vaccines, this research can help decrease vaccine hesitancy among menstruating individuals.

To assess the association between vaccination and menstrual alterations more precisely, a prospective evaluation before and after vaccination was required. Considering the chaos and anxiety that the COVID-19 era brought forth, this could not be planned. This study design can be conducted more systematically and prospectively in case similar situations occur in the future.

Conclusion

The following vaccination, approximately 50% of individuals reported having menstrual problems. It was found that BMI, smoking, IUDs, and pre-vaccination quantity number of pads used daily were independent risk factors for disordered menstruation.

Acknowledgments: I would like to thank our Gynecological Oncology Clinic Nurse Demet Tuğ for helping to collect data.

Ethics

Ethics Committee Approval: This study was approved by Ethics Committee of University of Health Sciences Turkey, Derince Training and Research Hospital, Non-Invasive Clinic Ethics Committee (approval date 27.10.22, institution review board number: 2022-92).

Informed Consent: Informed consent was obtained.

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Supplementery File 1.

Sizi bir formu doldurmaya davet ettim:

COVİD-19 BİONTECH AŞISI SONRASI ADET DÜZENİNİ DEĞERLENDİRME

Merhaba, bu anketi 18 yaş üstü kadınlarda Covid-19 Biontech aşısının adet düzenine etkisini değerlendirmek üzere oluşturduk. Size özel bilgileriniz kimseyle paylaşılmayacak olup, tüm sonuçların genel bir istatistiği yapılarak elde edilen sonuçlar yayınlanacaktır.
Teşekkürler.

YAŞINIZ * .....

KİLONUZ (KG) * .....

BOYUNUZ (CM) * .....

SİGARA KULLANIYOR MUSUNUZ? *

- o EVET
- o HAYIR

COVİD-19 HASTALIĞI GEÇİRDİNİZ Mİ?

- o EVET- BİONTECH İLE HİÇ AŞILANMAMIŞ İKEN
- o EVET- BİONTECH AŞISI OLDUKTAN SONRAKİ SÜREÇTE
- o HAYIR

EK HASTALIĞINIZ VAR MI? VARSA NEDİR *

KAN SULANDIRICI İLAÇ KULLANIYOR MUSUNUZ? *

- o EVET
- o HAYIR

NORMAL VEYA SEZARYEN TOPLAM KAÇ DOĞUM YAPTINIZ? *

HER AY DÜZENLİ ADET GÖRÜR MÜSÜNÜZ? *

- o EVET
- o HAYIR-SEYREK OLUR
- o HAYIR- SIK SIK OLURUM
- o HAYIR- HİÇ BELLİ OLMAZ
- o MENOPOZDAYIM

ADETİNİZ ORTALAMA KAÇ GÜN SÜRER?

ADET MİKTARINIZ NASIL, GÜNDE EN FAZLA KAÇ PED KULLANIRSINIZ BELİRTİNİZ ?

- o NORMAL (EN YOĞUN OLDUĞU GÜN EN ÇOK 2-3PED)
- o AZ (EN YOĞUN OLDUĞU GÜN 1 PEDİ DOLDURMAZ)
- o YOĞUN (GÜNDE 2-3PEDDEN FAZLA VEYA PIHTI HALİNDE KANAMA)

ADETLERİNİZDE AĞRINIZ OLUR MU?

- o EVET
- o HAYIR

GEBELİKTEN KORUNMAK İÇİN BİR ŞEY KULLANIYOR MUSUNUZ? *

- o HAYIR
- o DOĞUM KONTROL HAPI
- o SPİRAL
- o İLAÇLI SPİRAL (MİRENA)
- o Diğer:

KAÇ DOZ BİONTECH COVİD AŞISI OLDUNUZ? *

AŞI SONRASI ADET DÜZENİNİZDE BOZUKLUK-ARA KANAMA, LEKELENMENİZ OLDU MU? MENOPOZDAYSANIZ KANAMANIZ OLDU MU? *

- o EVET
- o HAYIR

Supplementery File 1. Continued

ADET KANAMA MİKTARINIZDA DEĞİŞİKLİK OLDU MU ?

- o HAYIR
- o EVET YOĞUNLAŞTI
- o EVET AZALDI
- o TAMAMEN KESİLDİ

ADET OLDUĞUNUZ GÜN SAYISI DEĞİŞTİ Mİ?

- o HAYIR
- o EVET UZADI VEYA ÖNCESİ-SONRASI LEKELENMELER OLUŞTU
- o ARA KANAMALARIM OLDU
- o EVET KISALDI
- o TAMAMEN KESİLDİ

KAÇINCI DOZDAN SONRA DEĞİŞİKLİK OLDU? *

- o OLMADI
- o İLK
- o 2.DOZDAN SONRA
- o 3.
- o BİRDEN FAZLA KEZ

AŞI SONRASI ADETLERİNİZDE AĞRI OLDU MU

- o EVET
- o HAYIR

EK YAN ETKİ OLDU MU? VARSA BELİRTİNİZ *

AŞI SONRASI DEĞİŞİKLİK NEDENİYLE KADIN-DOĞUM DOKTORUNA BAŞVURDUNUZ MU? *

- o EVET
- o HAYIR

BAŞVURDUYSANIZ BİR PROBLEM TESPİT EDİLDİ Mİ? *

- o BAŞVURMADIM
- o EVET SORUN SAPTANDI
- o HAYIR BİR SORUN SAPTANMADI

SORUN SAPTANDIYSA NEDİR?

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ORIGINAL RESEARCH

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Placenta Previa and Adverse Neonatal Outcomes in A Tertiary Center

Üçüncü Basamak Bir Merkezde Plasenta Previa ve Yenidoğan Olumsuz Sonuçları

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Abstract

Objective: Abnormal localization of the placenta with complete or partial closure of the cervix is called placenta previa. Placenta previa occurs in approximately 0.3-0.5% of pregnancies. In this study, we aimed to determine the risk factors and adverse fetal outcomes by comparing the neonatal outcomes of patients who underwent cesarean section for placenta previa with those of patients who underwent cesarean section for other indications.

Method: Patients with singleton pregnancies diagnosed with placenta previa were retrospectively analyzed. Placenta previa, risk factors, and adverse neonatal outcomes were estimated using multivariate logistic regression models.

Results: A total of 61,110 deliveries were analyzed, and 632 deliveries (288 patients, 344 controls) were included in the study. The prevalence of placenta previa was 0.47%. Advanced maternal age [odds ratio (OR)=3.03], multigravida (≥5) (OR=2.31), previous abortion (OR=1.58) and curettage (OR=2.32) were significant risk factors for placenta previa. However, these patients had an increased risk of 1st minute Apgar score <7 (OR=1.59) and neonatal intensive care unit (NICU) admission (OR=2.15). At the same time, the risk of Apgar score <7 at 1 min (OR=5.59) and 5 min (OR=3.94) and NICU admission (OR=28.47) increased in infants of patients with placenta previa <34 weeks. Newborns in the >37 weeks

Öz

Amaç: Plasentanın, serviksi tam ya da kısmen kapatarak anormal loklizasyonda olmasına plasenta previa denir. Plasenta previa, gebeliklerin yaklaşık %0,3-0,5'inde görülür. Bu çalışmada plasenta previa nedeniyle sezaryan olmuş hastaların yenidoğan sonuçları ile başka endikasyonlarla sezaryan olmuş hastaların yenidoğan sonuçları karşılaştırılarak risk faktörleri ve olumsuz fetal sonuçları tespit etmeyi amaçladık.

Yöntem: Plasenta previa tanısı almış tekil gebeliği olan hastalar retrospektif olarak analiz edildi. Plasenta previa, risk faktörleri ve bu durumun oluşturabileceği olumsuz neonatal sonuçlar çok değişkenli lojistik regresyon modelleri ile tahmin edildi.

Bulgular: Toplam 61.110 doğum analiz edilmiş ve 632 doğum (288 hasta, 344 kontrol) çalışmaya dahil edilmiştir. Plasenta previa prevalansı %0,47 idi. İleri anne yaşı [olasılık oranı (OO)=3,03], multigravida (≥5) (OO=2,31), önceki abortus (OO=1,58) ve küretaj (OO=2,32) plasenta previa risk faktörleri için anlamlı bulunmuştur. Bununla beraber bu hastalarda 1. dakika Apgar skoru <7 (OO=1,59) ve yenidoğan yoğun bakım ünitesine (YYBÜ) (OO=2,15) kabul riski artmıştır. Aynı zamanda <34 hafta hafta olan plasenta previa bulunan hastaların bebeklerinde 1. dakikada (OO=5,59) ve 5. dakikada (OO=3,94) Apgar skorunun <7 olması ve YYBÜ'ye kabul (OO=28,47) riski artmıştır. Plasenta previa bulunan >37 haftalık gebelik yaşı grubundaki yenidoğanların daha düşük doğum ağırlığına (OO=4,21)

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Abstract

gestational age group with placenta previa were more likely to have a lower birth weight (OR=4.21) and an Apgar score <7 at 5 min (OR=1.89).

Conclusion: Pregnancies with a diagnosis of placenta previa were associated with an increased risk of serious fetal outcomes compared with cesarean deliveries for all other indications, regardless of delivery timing.

Keywords: Neonatal, outcome, placenta previa

Öz

ve 5. dakikada <7 Apgar skoruna (OR=1,89) sahip olma olasılığı daha yüksektir.

Sonuç: Plasenta previa tanısı konan gebelikler, doğum zamanlamasından bağımsız olarak, diğer tüm endikasyonlar için sezaryen ile yapılan doğumlara kıyasla ciddi fetal sonuç riski ile ilişkilendirilmiştir.

Anahtar kelimeler: Neonatal, plasenta previa, sonuç

Introduction

In obstetrics, implantation of the placenta in an abnormal location close to the uterine isthmus, just above or near the internal os, is called placenta previa (1). This condition can be observed in approximately 0.3-0.5% of all pregnancies, and this rate has increased in the last 30 years (2). Although there are different opinions regarding the etiology, the exact cause has not been established. However, it has been associated with well-established demographic factors such as advanced maternal age (3), multiparity (4), smoking, and cocaine use (5) as well as clinical features such as one or more cesarean deliveries (6), previous uterine incision (7), placenta previa in previous pregnancy (8), multiple pregnancy (9) and use of assisted reproductive techniques (10).

Pregnant women with placenta previa may have adverse maternal complications such as death, maternal hypovolemia, blood transfusion, and emergency hysterectomy due to severe bleeding (11), and their newborns have an increased risk of low birth weight (LBW), fetal anomalies, stillbirth, and early neonatal death (12). Women with placenta previa are managed according to their clinical condition; however, almost all women with placenta previa and no bleeding undergo planned prophylactic preterm cesarean delivery, which balances the risks of maternal antepartum bleeding and fetal immaturity. The Society for Maternal Fetal Medicine (SMFM) recommends waiting until 36-37 6/7 weeks of gestation for delivery, especially in stable patients without bleeding and other obstetric complications (Level of Evidence: Grade 1B) (13).

In our study, we aimed to investigate whether placenta previa alone is a risk factor for neonatal outcomes by comparing the neonatal outcomes of patients who were followed up for placenta previa and who underwent cesarean delivery with those of patients who underwent cesarean delivery for all other indications; both groups included preterm deliveries. Understanding this will allow us to better manage and prevent adverse neonatal outcomes.

Materials and Methods

This was a retrospective cohort study of women with singleton pregnancies who delivered between January 2012 and December 2015 at our institution, a tertiary referral hospital. Data were retrieved from the local perinatal database, medical documentation system, or patient files. This study was approved by the institutional review board. Ethical approval was obtained from the Ethics Committee University of Health Sciences Turkey, İstanbul Kanuni Sultan Süleyman Training and Research Hospital (date: 02.05.2015, number: 2014/10). Written informed consent was obtained from all patients and controls.

We recruited all patients with a definitive diagnosis of placenta previa who underwent cesarean section due to placenta previa. Placenta previa was defined as the placenta covering all or part of the internal os, as diagnosed through ultrasound during the second or third trimester, and the diagnosis was confirmed at cesarean delivery. The control group comprised healthy pregnant individuals without placenta previa who underwent elective cesarean section for all other indications. Patients with incomplete data in their medical files, multiple pregnancies, chronic disease, and fetuses with major congenital anomalies were excluded.

Demographic data including maternal age, obstetric history (gravidity, parity, prior cesarean section/vaginal delivery/abortion/curettage), and neonatal outcome variables [gestational age at delivery, birth weight, Apgar score at minute 1, Apgar score at minute 5, and neonatal intensive care unit (NICU) admission] were recorded. Gestational age was based on the last menstrual period, first-trimester ultrasound, or both. LBW was defined as a birth weight of 2500 g (up to and including 2499 g). The Apgar score was

defined as a measure of the physical condition of a newborn infant. The Apgar score has maximum ten points, with two points possible for each heart rate, muscle tone, response to stimulation, and skin coloration. Apgar scores between 0 and 6 were recorded as low Apgar scores. NICU admission was considered when infants were intubated.

The study population was initially divided into two groups: Those born by cesarean section because of placenta previa (patient group) and those born by cesarean section for all other indications (control group). Both groups were further stratified into three subgroups based on the gestational age because studies (14) have consistently shown higher neonatal mortality and morbidity in preterm infants: <34 weeks, 34-36 weeks, and ≥37 weeks. The incidence of adverse neonatal outcomes was examined in each group.

Statistical Analysis

NCSS 10 statistical software (Kaysville, Utah, USA) was used for data recording and statistical analysis. Statistical analyses were performed using descriptive statistics, independent samples t-test, and Mann-Whitney U test, when appropriate, applying a significance level of $p<0.05$. Categorical variables were analyzed using the chi-square test and Yates's chi-square test. Covariance analysis was performed, and the variables found to differ were reanalyzed because the age variable was different between the groups. Variables are given as mean, standard deviation, median, minimum, maximum, frequency, and percentage.

Results

In our study, a total of 61,110 deliveries were evaluated, and 288 of them (0.47%) were diagnosed with previa. placenta Apart from this group, 344 control patients were included in the study, and the total number of patients participating in the study was 632. The mean age of pregnant women complicated with previa was significantly higher than that of the control group. Similarly, gravida, parity, previous curettage, and curettage rates were also found to be significantly higher ($p=0.001$, $p=0.048$, $p=0.014$ and $p=0.007$, respectively). The percentage of previous cesarean section was significantly higher in the control group ($p<0.001$); however, the mean number of cesarean sections was similar for both groups (1.2±1.01 for the patient group and 1.1±0.73 for the control group, $p=0.869$). Demographic data and risk factors of all patients and the control group participating in the study are shown in Table 1.

In our study, it was observed that patients complicated with placenta previa were older than those who underwent cesarean section for all other reasons. Pregnancies complicated with placenta previa were significantly more common in multigravida women in the <34 weeks and ≥37 weeks gestational age groups and higher in the 34-36 weeks group. Previous miscarriage was significantly more frequent in the <34 weeks group and previous curettage was significantly more frequent in the 34-36 weeks group. As in the main groups, previous cesarean section was more common in all control groups, reaching statistical significance in the <34 weeks and ≥37 weeks groups ($p=0.004$ for each). However, the mean number of cesarean sections was not significantly higher in either previa group (1.4±1.25 vs. 1.1±0.61, $p=0.193$ in the <34 weeks group and 1.11±0.962 vs. 1.09±0.656, $p=0.843$ in the ≥37 weeks group). The demographic characteristics and risk factors of the subgroups in our study are shown in Table 2.

After adjusting for the factors that may cause differences between the two groups, advanced maternal age (≥35 years) [odds ratio (OR) =3.03; 95% confidence interval (CI): 1.99-4.59], multigravida (≥5) (OR=2.31; 95% CI: 1.43-3.73), previous abortion (OR=1.58; 95% CI: 1.10-2.25) and previous curettage (OR=2.32; 95% CI: 1.26-4.29) were found to be significant risk factors for placenta previa. History of vaginal delivery or previous cesarean section was not

Table 1. Maternal characteristics in pregnancies with and without placenta previa

	Placenta previa group (n=288)	Control group (n=344)	p
Maternal age at index birth (years)	31.5±5.14	28.5±5.19	**<0.001**
Gravidity	3.1±1.45	2.8±1.25	**0.001**
Parity	1.5±1.11	1.4±0.98	**0.048**
Previous cesarean section	69.4%	82.8%	**<0.001**
Previous vaginal delivery	20.5%	16.3%	0.180
Previous abortion	30.9%	22.1%	**0.014**
Previous curettage	10.8%	4.9%	**0.007**

All values are expressed as mean ± SD and percentage, where appropriate, SD: Standard deviation

significantly associated with placenta previa. Neonates in the patient group were more likely to have a 1st minute Apgar score below 7 (OR=1.59; 95% CI: 1.05-2.41) and to be admitted to the neonatal intensive care unit (OR=2.15; 95% CI: 1.53-3.02). Apgar score below 7 in 5 min and LBW were not associated with placenta previa (Table 3). In the <34 weeks placenta previa group, the probability of having a 1st minute Apgar score below 7 (OR=5.59; 95% CI: 2.32-13.48), the probability of having a 5th minute Apgar score below 7 (OR=3.94; 95% CI: 1.17-13.28) and the probability of being admitted to the NICU increased (OR=28.47; 95% CI: 7.7-105.28). In the >37 weeks placenta previa group, LBW (OR=4.21; 95% CI: 1.36-13.08) and 5th minute Apgar score below 7 were more likely (OR=1.89; 95% CI: 1.71-2.09) (Table 4).

Discussion

In our study, we compared the neonatal outcomes after cesarean section performed in patients complicated by placenta previa with the neonatal outcomes of patients who underwent cesarean section for all other indications. We found statistically significantly higher maternal age, gravida, previous abortion, and curettage rates in the patient group. We found that neonates in the patient group had a lower 1st minute Apgar score and a higher risk of NICU admission. This demonstrated that placenta previa is a negative risk factor for neonatal outcomes regardless of gestational week, especially in the <34 weeks gestation group. A 5-min Apgar score below 7 and LBW neonatal outcomes were not associated with placenta previa in the study groups. Although there are some differences, these data are complementary and contribute to studies evaluating perinatal outcomes in pregnancies complicated with placenta previa.

Abnormal localization of the placenta and partial or complete closure of the cervical canal is called placenta previa. Although some studies have shown the incidence to be 1% (16), most studies have shown the incidence to be 0.3-0.5% in general (2,15), and we found 0.47% in our study, which is consistent with the literature. Although a published meta-analysis showed that the previa rate was affected by regional differences (17), another study with a longer duration and a larger scope showed a prevalence similar to that in our study (16).

Table 2. Maternal characteristics in pregnancies with and without placenta previa based on gestational age at delivery

	<34 weeks			34-36 weeks			≥37 weeks		
	Placenta previa (n=47)	Controls (n=50)	p	Placenta previa (n=80)	Controls (n=113)	p	Placenta previa (n=161)	Controls (n=181)	p
Maternal age at index birth (years)	30.4±5.48	28.1±4.37	**0.029**	31.7±5.22	28.5±5.37	**<0.001**	31.8±5.00	28.6±5.31	**<0.001**
Gravidity	3.1±1.62	2.5±0.81	**0.020**	3.3±1.51	2.9±1.52	0.097	3.1±1.39	2.8±1.16	**0.018**
Parity	1.7±1.33	1.3±0.77	0.109	1.6±1.24	1.4±1.19	0.177	1.4±0.97	1.4±0.88	0.527
Previous cesarean section	68.1%	92.0%	**0.004**	68.8%	77.9%	0.183	70.2%	83.4%	**0.004**
Previous vaginal delivery	21.3%	24.0%	0.811	23.8%	14.2%	0.128	18.6%	15.5%	0.472
Previous abortion	27.7%	8.0%	**0.015**	27.5%	25.7%	0.869	33.5%	23.8%	0.054
Previous curettage	4.3%	4.0%	>0.999	17.5%	5.3%	**0.008**	9.3%	5.0%	0.139

Table 3. Neonatal outcomes in pregnancies with and without placenta previa

	Placenta previa group (n=288)	Control group (n=344)	p
Gestational age at delivery, weeks	35.9±2.97	35.9±2.40	0.788
Sex, male			-
Birth weight (g)	2745.7±709.21	2980.3±711.12	**<0.001**
Low birth weight	29.5%	25.0%	0.209
Apgar score at minute 1	7.3±1.67	7.5±1.60	0.153
Apgar-score <7	20.5%	14.0%	**0.033**
Apgar score at minute 5	8.8±1.14	9.1±0.98	**<0.001**
Apgar-score <7	5.2%	3.5%	0.326
Neonatal intensive care unit admission	41.0%	24.4%	**<0.001**

Table 4. Maternal characteristics in pregnancies with and without placenta previa based on gestational age at delivery

	<34 weeks			34-36 weeks			≥37 weeks		
	Placenta previa (n=47)	Controls (n=50)	p	Placenta previa (n=80)	Controls (n=113)	p	Placenta previa (n=161)	Controls (n=181)	p
Gestational age at delivery, weeks	30.3±2.61	31.2±1.97	0.078	35.4±0.82	35.4±0.68	0.923	37.7±0.95	37.6±0.63	0.084
Sex, male									
Birth weight (g)	1650.9±533.16	2004.8±354.08	**<0.0001**	2681.8±526.79	2690.4±531.40	0.912	3097.0±452.89	3430.8±482.27	**<0.001**
Low birth weight	93.6%	100%	0.110	33.8%	28.3%	0.432	8.7%	2.2%	**0.013**
Apgar score at minute 1	5.5±1.96	7.3±1.56	**<0.001**	7.3±1.62	7.1±1.95	0.483	7.9±1.16	7.8±1.27	0.758
Apgar-score <7	63.8%	24.0%	**<0.001**	17.5%	19.5%	0.852	9.3%	7.7%	0.698
Apgar score at minute 5	7.4±1.61	8.5±0.93	**<0.001**	8.9±0.88	8.9±1.18	0.753	9.2±0.66	9.4±0.75	**0.010**
Apgar-score <7	25.5%	8.0%	**0.028**	3.8%	6.2%	0.527	0%	0.6%	>0.999
Neonatal intensive care unit admission	93.6%	34.0%	**<0.001**	42.5%	32.7%	0.176	24.8%	16.6%	0.062

Each woman with placenta previa is managed according to her clinical characteristics; however, most women with placenta previa undergo elective prophylactic preterm cesarean section. In stable patients, the SMFM recommends waiting for delivery until 36-37 6/7 weeks of gestation (13). After 37 weeks, approximately 40-50% of deliveries are planned after this week because the concern of prematurity disappears (18). In our study, this rate was found to be 55.9%, which is higher than the literature.

Our study findings are compatible with the literature regarding risk factors for placenta previa, including advanced maternal age, increased gravidity, and previous abortion and curettage (1). It has been suggested that advanced maternal age has an effect on the risk of placenta previa formation (2) independent of other known risk factors due to age-related insufficient perfusion and insufficient vascularization (1). In contrast to our results, some other studies have reported that advanced maternal age was not associated with placenta previa (19). Many opinions have been put forward to demonstrate the relationship between gravida, parity, curettage, abortion history, and previa. During pregnancy, the endometrium in which the gestational material is implanted may be damaged, and vascularization may change, which may lead to inadequate nutrition of the placenta by creating unsuitable regions for implantation and increase the possibility of implantation in the lower segment (20). Some studies found that the risk of previa increased 2.3-fold with multigravida (≥5) (19), some found no association (21,22), and some found that although there was an association, the risk did not increase significantly (23). In our study, we did not find a significant association between placenta previa and multiparity.

According to data from previous studies, there is a significant association between the number of previous cesarean sections and placenta previa (24). Interestingly, unlike previous studies (6,25), the number of previous cesarean sections was more common in the control group; however, in this study, the mean number of cesarean sections was similar for both groups and the history of previous cesarean section was not associated with placenta previa, similar to some other studies (19).

It has been reported that women reporting one or more abortions are 30% more likely to encounter placenta previa than women without a history of abortion (26). In our study, the abortion rate was significantly higher in patients with placenta previa (30.9% vs. 22.1%, p=0.014) (OR=1.58), which was consistent with previous data (27). The rate of

prior curettage in the patients in our study was similar to that in other studies (10.8% vs. 4.9%, p=0.007) (OR=2.32) (28).

Schneiderman and Balayla (29) suggested, as we planned to do, that to fully understand the neonatal outcomes of pregnant women complicated with placenta previa, they should not be compared with the outcomes of patients who had vaginal deliveries but with those of patients who had cesarean deliveries for all other indications. In addition, because neonatal morbidity can be greatly affected by gestational age, we also performed a subgroup analysis based on gestational age. Thus, in our study, we could determine whether placenta previa could be a risk factor for newborns regardless of gestational age.

Studies have examined the relationships among prematurity, LBW, postpartum respiratory depression, respiratory distress syndrome (RDS), low Apgar scores, and placenta previa (30,31). Prematurity is a risk factor for unfavorable outcomes. In our study, the rate of prematurity was found to be 44.1% (gestational week <37 weeks). We believe that this is related to elective planned preterm delivery. Although studies have shown that fetal oxygenation and growth are affected by abnormal placental positioning, some studies have conflicting results between placenta previa and fetal development. Although there are reports of intrauterine growth retardation related to the link between these two conditions (15,32), this link has not been demonstrated in some reports (12,33).

Regarding fetal weight, although mean newborn body weights were higher in the patient group (p<0.001), LBW was not associated with placenta previa in the entire study group; we found significantly higher LBW rates in the >37 weeks gestational age group with an OR of 4.21 (8.7% vs. 2.2%, p=0.013). This finding contradicts the idea that placenta previa negatively affects newborn weight after adjusting for gestational age (34). In the group of patients with previa, neonatal Apgar scores are more likely to be below 7 (12).

In this study, significant differences were found between the two groups in the rates of Apgar score <7 at 1 min and mean Apgar score at 5 min. However, Apgar score <7 at 5 min was not associated with placenta previa in the whole study group. When subgroups were evaluated, in pregnancies below 34 weeks of gestation, the probability of having a 1st minute Apgar score below 7 (OR=5.59) and the probability of having a 5th minute Apgar score below 7 increased in the group complicated with placenta previa (OR=3.94). Neonates with a gestational age >37 weeks had a higher probability of having a 5th minute Apgar score below 7 (OR=1.89).

According to a published meta-analysis, NICU admission is five times higher in pregnant women complicated with placenta previa than in other pregnant women (35). It is thought that the intrauterine conditions of the newborn predispose the newborn to hypoxia and anemia, thus increasing the incidence of RDS and NICU admission (30). In our study, it was found that neonates of pregnant women complicated with placenta previa were more likely to be admitted to the NICU (OR=2.15); likewise, the likelihood of neonatal admission to the NICU increased in deliveries of these patients before the 34th gestational week (OR=28.47).

Study Limitations

The retrospective nature of our study and the lack of information about complicated cases, infertility treatment, and their outcomes are the limitations of our study. Prospective studies that minimize these limitations may contribute to the literature. The greatest strength of the study is the comparison of neonatal outcomes of pregnant women complicated with placenta previa with cesarean deliveries for all other indications, thus ruling out the higher risk of adverse neonatal outcomes with cesarean delivery compared with vaginal delivery, and the subgroup analysis based on gestational week because neonatal morbidity can be greatly affected by gestational week.

Conclusion

We conclude that pregnancies with a diagnosis of placenta previa are associated with an increased risk of serious fetal outcomes compared with cesarean deliveries for all other indications, regardless of the timing of delivery.

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Ethics

Ethics Committee Approval: This study was approved by the institutional review board. Ethical approval was obtained from the Ethics Committee University of Health Sciences Turkey, İstanbul Kanuni Sultan Süleyman Training and Research Hospital (date: 02.05.2015, number: 2014/10).

Informed Consent: Written informed consent was obtained from all patients and controls.

Authorship Contributions

Surgical and Medical Practices: M.B., V.A.T., A.E., A.B., O.K., Concept: M.B., İ.P., Design: M.B., V.A.T., A.E., A.B., O.K., D.Y., İ.P., Data Collection or Processing: M.B., V.A.T., A.B., O.K., D.Y., İ.P., Analysis or Interpretation: M.B., V.A.T., A.E., A.B., O.K., D.Y., İ.P., Literature Search: M.B., V.A.T., Writing: M.B., V.A.T., A.E., A.B., O.K., D.Y., İ.P.

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ORIGINAL RESEARCH

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Twelve-year Experience for Tenosynovial Giant Cell Tumors of Tendon Sheath: A Review of 95 Cases from A Single Institution

Tendon Kılıfının Tenosinovyal Dev Hücreli Tümörlerinde 12 Yıllık Deneyim: Tek Bir Kurumdan 95 Olgunun Gözden Geçirilmesi

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Abstract

Objective: We aimed to present our 12-year experiences for tenosynovial giant cell tumors (TGCTs) of tendon sheath by summarizing the demographic characteristics and clinicopathological features of 95 cases who underwent excision of localized TGCT in a single institution to investigate the factors associated with gender and tumor location among the patients.

Method: The medical records of 95 patients with TGCT were reviewed. Demographic characteristics and clinicopathological findings were collected and compared according to gender and tumor location.

Results: Females were predominantly involved (78.95%). The mean age was 41.09±14.26 years. The majority of patients had TGCT in their hands (75.79%) and most predominantly involved tumors in D1 and D2 (n=21 and 25, respectively). The tumor invaded into the bone/joint of 5 patients (5.26%), and 4 recurrences (4.21%) were determined over the mean follow-up period of 84.3 months (range: 14-136). No significant difference was found in demographics and clinicopathological features between two genders (p>0.05). However, there was a significant increase in the median tumor size of male patients compared with that of females (p=0.011). There was also no significant difference in demographics and clinicopathological features among digits of hands (p>0.05).

Conclusion: Our study provides a comprehensive analysis of 95 patients who underwent surgical resection for localized TGCTs over 12 years at a single tertiary care hospital. TGCTs pose unique challenges in management because of their diverse clinical presentations and variable recurrence rates. Despite being predominantly benign, TGCTs exhibit recurrence and bone/joint invasion, necessitating meticulous follow-up and evaluation.

Keywords: Gender, recurrence, tenosynovial giant cell tumors, tumor location

Öz

Amaç: Tendon kılıfının tenosinovyal dev hücreli tümörlerinde (TGCT) 12 yıllık deneyimimizi, tek bir kurumda lokalize TGCT eksizyonu yapılan 95 olgunun demografik özelliklerini ve klinikopatolojik özelliklerini özetleyerek sunmayı ve hastalar arasında cinsiyet ve tümör yerleşimi ile ilişkili faktörleri araştırmayı amaçladık.

Yöntem: TGCT'li 95 hastanın tıbbi kayıtları gözden geçirildi. Demografik özellikler ve klinikopatolojik bulgular toplandı ve cinsiyet ve tümör yerleşimine göre karşılaştırıldı.

Bulgular: Kadınların çoğunlukta olduğu görüldü (%78,95). Ortalama yaş 41,09±14,26 yıl idi. Hastaların çoğunluğu ellerde TGCT'ye sahipti (%75,79) ve en sık D1 ve D2'de tümör tutulumu vardı (sırasıyla n=21 ve 25). Ortalama 84,3 aylık (aralık: 14-136) takip süresi boyunca 5 hastada (%5,26) tümör kemiğe/ekleme invaze olmuş ve toplam 4 nüks (%4,21) tespit edilmiştir. İki cinsiyet arasında demografik ve klinikopatolojik özellikler açısından anlamlı bir fark bulunmamıştır (p>0,05). Bununla birlikte, erkek hastaların medyan tümör boyutunda kadınlara göre anlamlı bir artış vardı (p=0,011). El parmakları arasında da demografik ve klinikopatolojik özellikler açısından anlamlı bir fark yoktu (p>0,05).

Sonuç: Çalışmamız, bir üçüncü basamak hastanede 12 yıllık süre boyunca localize TGCT'ler için cerrahi rezeksiyon uygulanan 95 hastanın kapsamlı bir analizini sunmaktadır. TGCT'ler, çeşitli klinik tabloları ve değişken nüks oranları nedeniyle tedavide benzersiz zorluklar oluşturmaktadır. Çoğunlukla benign olmalarına rağmen, nüks ve kemik/eklem invazyonu sergileyen TGCT'ler titiz takip ve değerlendirme gerektirir.

Anahtar kelimeler: Cinsiyet, nüks, tenosinovyal dev hücreli tümörler, tümör yerleşimi

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Introduction

According to the World Health Organization classification of tumors, tenosynovial giant cell tumors (TGCTs) are a group of benign soft tissue tumors with neoplastic, inflammatory, trauma-related, immune-mediated, or abnormal lipid metabolism. TGCTs originate from the synovial cells of the tendon sheath, synovium of joints or bursae (1). TGCT is the most common tumor in the foot and the second most common tumor in the hand following the ganglion cysts (1,2).

TGCT is classified into two different types, localized and diffuse, according to their growth characteristics (3). The diffuse type, also known as pigmented villonodular synovitis, tends to be multinodular and intraarticular, presenting an aggressive clinical course, and recurrence rates are crucially high among patients (4). The localized type tends to be less aggressive, often involving the tendon sheaths as a single nodular lesion (5). A surgical resection is the standard treatment modality in the localized type, whereas the ideal treatment modality in the diffuse type is controversial (6).

Although TGCT is typically non-cancerous, recurrence rates can reach as high as 15% (7). Several factors associated with elevated recurrence rates have been identified in the literature, including the diffuse type (8), bone erosion, joint arthritis (9,10), involvement of neurovascular structures (11), incomplete resection (12), tumor invasion beyond the capsule (13), and lesion size exceeding 2 cm (14). However, the available literature lacks sufficient clarity on the factors that are most influential in causing recurrence. Many studies included in the literature did not adhere to a standardized surgical protocol, and there are limited data comparing findings based on gender. Additionally, recurrence rates varied among studies due to differences in follow-up periods and a significant number of lost patients, making comparisons challenging (5,7,9-14). Therefore, we aimed to present our 12-year experience with TGCTs by presenting the demographic characteristics and clinicopathological features of 95 cases who underwent excision of localized TGCT in a single institution to investigate the factors associated with gender and tumor location among the patients.

Materials and Methods

Patient Selection

The data of 95 patients who underwent surgical procedures at our orthopedics and traumatology clinic and were diagnosed with TGCT between 2010 and 2022 were retrospectively reviewed using hospital records and subsequently incorporated into the study. The investigation was conducted at a single tertiary care hospital, with the research protocol receiving approval from an Institutional Review Board of University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital (ethics committee protocol number: 2023/09/13/056). Inclusion criteria comprised patients aged 18 years or older, with a histologically confirmed diagnosis of localized tendon sheath tumor, and a minimum follow-up duration of 2 years. Patients lacking adequate follow-up documentation or exhibiting suspicious pathological diagnoses were excluded from the study. Initially, a pool of 108 potentially eligible patients was identified from hospital records. However, five patients were lost to clinical follow-up, records for three patients' last examinations were unavailable, and five patients were omitted because of diagnostic ambiguities. Consequently, the final cohort consisted of 95 patients diagnosed with TGCT, all of whom underwent surgery by a single surgeon within the orthopedic clinic of the aforementioned tertiary care hospital and had undergone clinical follow-up.

Data Collection

A standardized database sheet including the demographics, preoperative radiological findings, detailed operative notes and physical examination of the lesion was created using hospital records. The records included the age, gender, anatomical localization of the tumour, its relationship with structures such as bone and nerve, invasion to the bone/jointand preoperative duration after the onset of symptoms, postoperative complication as recurrence.

Operation

All patients were operated on by the same surgeon. Incisions on the relevant anatomical region of the lesion were made during surgery according to the principles of oncological surgery. The masses were removed in one piece with maximum attention to the adjacent important structures, ensuring that there were no satellite lesions, and were preserved for pathological examination.

Pathology

Pathological examination of lesions was performed by a single pathologist. The maximum diameter and appearance of the masses were recorded macroscopically. Routine tissue preparation techniques, hematoxylin & eosin staining and immunohistochemical studies were applied to the tissues, and the diagnosis of TGCT was confirmed microscopically. Data were included in the records.

Follow-up

Following the surgeries, passive movement initiation started within the first week, with active movement initiation following pain alleviation in the second week. Sutures were removed after a 14-day period, and patients were scheduled for subsequent follow-up appointments. During these appointments, complications including recurrence, joint motion restriction, neurovascular assessments, and wound site issues were documented. The follow-up duration for the patients ranged from 14 to 136 months.

Statistical Analysis

Statistical analysis was performed using the GraphPad Instat ver. 3.06 (GraphPad Inc, CA, USA) computer program. The distribution of the variables was tested using Kolmogorov-Smirnov test. Normally distributed two continuous variables were compared using the unpaired t-test, and more than two variables were compared using One-Way Analysis of Variance. Not normally distributed two continuous variables were compared by Mann-Whitney U test and more than two variables by Kruskal-Wallis test. Categorical variables were compared using the chi-square test or chi-squared test for Independence. The statistical significance level was $p<0.05$.

Results

A total of 95 patients underwent surgical resection of localized TGCTs in our tertiary hospital between 2010 and 2022. The demographics and clinicopathological features of all patients are presented in Table 1. The mean age of all patients at the time of operation was 41.09±14.26 years (range: 18-68 years). 21.05% of patients were male. Of the total, 72 patients had tumors in the hand (75.79%), 13 had tumors in the foot (13.68%), 6 in the joint (6.31%), and 4 in the knee (4.21%). The right side was involved in 56.84% of patients (n=54). The surgeries were performed at mean 12 months (range: 3-60 months) after the onset of symptoms. The median largest dimension of the tumors was 1.7 cm (range: 0.5-8.5 cm). The tumor invaded the bone/joint of 5 patients (5.26%), and 4 recurrences (4.21%) were determined over the mean follow-up period of 84.3 months (range: 14-136 months) (Figures 1-3).

The demographics and clinicopathological features of patients were compared according to gender, and the results are presented in Table 2. No significant difference was found in the mean age, median preoperative duration, distribution of tumor location, side, and frequencies of bone invasion and recurrence between two genders ($p>0.05$). However, there was a significant increase in the median tumor size of male patients compared with that of females ($p=0.011$).

The demographics and clinicopathological features of patients were also compared according to the anatomic location of tumors in the hands, and the results are presented in Table 3. Twenty-one patients had TGCT in the D1 digit of the hand, 25 patients had TGCT in D2, 14 patients had one in D3, 7 patients in D4, and 5 patients in D5. No significant difference was found in the mean age, median preoperative duration and tumor size, distribution of gender, side of tumor location, and frequencies of bone invasion and recurrence among digits of hands ($p>0.05$).

Table 1. Demographics and clinicopathological features of the patients

		Total (n=95)
Age, mean ± SD	Year	41.09±14.26
Gender, n (%)	Male Female	20 (21.05) 75 (78.95)
Tumor location, n (%)	Hand Knee Foot Joint	72 (75.79) 4 (4.21) 13 (13.68) 6 (6.31)
Side, n (%)	Left Right	41 (43.16) 54 (56.84)
Tumor size, median [range]	Largest dimension (cm)	1.7 [0.5-8.5]
Bone invasion, n (%)		5 (5.26)
Preoperative duration, median [range]	Months	12 [3-60]
Recurrence, n (%)		4 (4.21)

SD: Standard deviation

Table 2. Comparison of demographics and clinicopathological features of patients according to gender

		Male (n=20)	Female (n=75)	p-value
Age, mean ± SD	Year	43.05±14.92	40.47±14.14	0.235
Tumor location, n (%)	Hand Knee Foot Joint	14 (70.0) 1 (5.0) 3 (15.0) 2 (10.0)	58 (77.33) 3 (4.0) 10 (13.33) 4 (5.33)	0.867
Side, n (%)	Left Right	7 (35.0) 13 (65.0)	34 (45.33) 41 (54.67)	0.565
Tumor size, median [range]	Largest dimension (cm)	2.5 [1.0-8.5]	1.5 [0.50-8.0]	**0.011**
Bone invasion, n (%)		2 (10.0)	3 (4.0)	0.614
Preoperative duration, median [range]	Months	12 [3-30]	12 [3-60]	0.982
Recurrence, n (%)		1 (5.0)	3 (4.0)	0.843

SD: Standard deviation

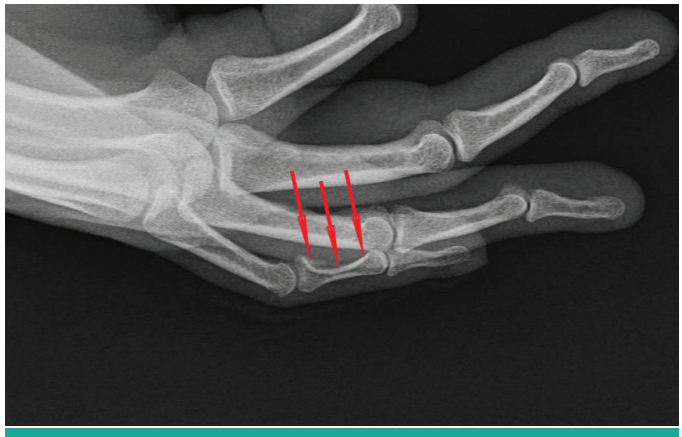

Figure 1. Bone erosion. Anteroposterior radiograph of fifth finger showing TGCT

TGCT: Tenosynovial giant cell tumor

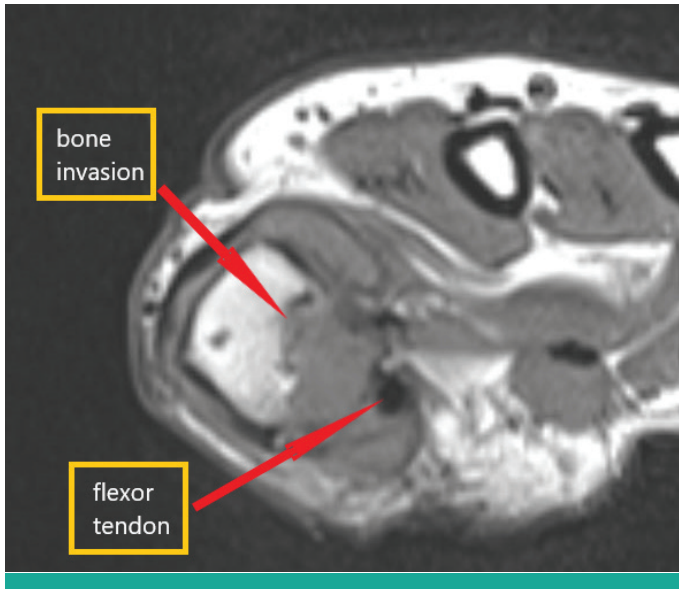

Figure 2. Intraosseous invasion. Magnetic resonance images of the thumb

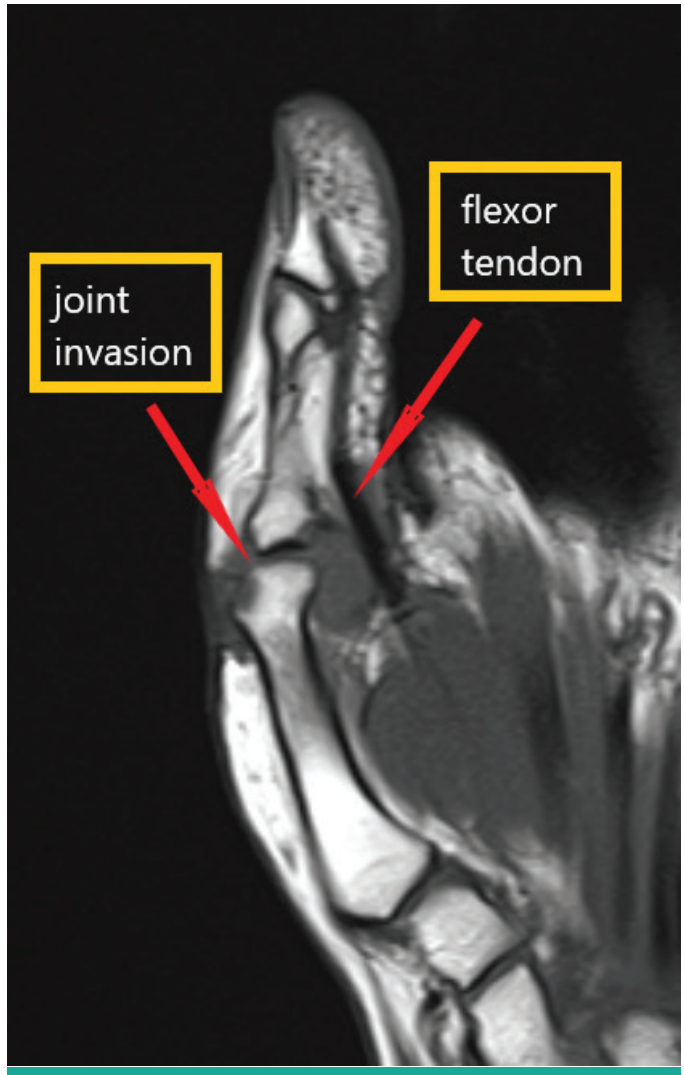

Figure 3. Joint invasion. Magnetic resonance images of thumb metacarpophalangeal joint

Table 3. Comparison of demographics and clinicopathological features of patients according to the anatomic location of tumors in hands

		D1 (n=21)	D2 (n=25)	D3 (n=14)	D4 (n=7)	D5 (n=5)	p-value
Age, mean ± SD	Year	46.9±9.9	38.8±14.5	46.2±12.0	43.3±9.9	50.0±12.4	0.135
Gender, n (%)	Male Female	2 (9.5) 19 (90.5)	7 (28.0) 18 (72.0)	1 (7.1) 13 (92.9)	2 (28.6) 5 (71.4)	2 (40.0) 3 (60.0)	0.234
Side, n (%)	Left Right	10 (47.6) 11 (52.4)	13 (52.0) 12 (48.0)	6 (42.9) 8 (57.1)	1 (14.3) 6 (85.7)	2 (40.0) 3 (60.0)	0.510
Tumor size, median [range]	Largest dimension (cm)	1.7 [0.9-8.0]	1.7 [0.5-3.0]	1.5 [1.0-2.6]	2.3 [1.0-3.0]	1.8 [1.0-2.5]	0.752
Bone invasion, n (%)		2 (9.5)	0 (0)	0 (0)	1 (14.3)	1 (20.0)	0.205
Preoperative duration, median [range]	Months	11 [4-60]	10 [3-24]	10.5 [3-26]	9 [5-48]	15 [9-24]	0.608
Recurrence, n (%)		1 (4.8)	0 (0)	0 (0)	0 (0)	1 (20.0)	0.130

SD: Standard deviation

Discussion

Despite the extensive literature on TGCTs of the tendon sheath, their treatment remains challenging for orthopedists. These tumors, which originate from synovial cells, can infiltrate nearby structures such as joints, bone cortices, tendon sheaths, and neurovascular tissues. Achieving a balance between complete tumor removal and preservation of vital tissues presents a significant challenge. In this study, we shared our institutional experience spanning 12 years with TGCTs of the tendon sheath and summarized the demographic characteristics and clinicopathological features of 95 cases who underwent localized TGCT excision. Our findings revealed an overall recurrence rate of 4.21%, with tumor size demonstrating variation based on gender, suggesting a potential risk factor for tumor growth in males.

There are various case series and case reports of benign and malignant soft tissue tumors (15). The literature presents several recurrence rates for TGCTs, from as low as 2% to as high as 24% (2,11,16,17). In our study, we attribute our relatively low recurrence rate of 4.21% to adherence to the principles of tumor surgery, frequent encounters with such cases in our tertiary center, and the expertise of our surgeons.

In line with previous studies (11,16), our observations regarding the anatomical distribution of TGCTs in the hand corroborate the existing literature, with a higher incidence noted in the first two fingers compared with others. While some studies have reported increased recurrence rates in specific joints, such as the distal interphalangeal and thumb interphalangeal joints (16), we did not observe such a relationship in our cohort.

Several studies have investigated the impact of the involvement of important structures on recurrence (18,19). Kitagawa et al. (18) reported an association between tumor proximity to neurovascular structures and recurrence, whereas Williams et al. (19) found that joint capsule involvement increased the recurrence rate to 32%. In our study, although we observed bone and joint invasion in one patient with recurrence, we did not find a statistically significant association.

According to multiple studies, TGCTs exhibit female gender predominance (20). Consistent with existing literature, our patient series also demonstrated a high proportion of female patients. However, while previous research indicates no significant correlation between tumor size and gender, our analysis revealed a significantly larger tumor size among male patients, despite comparable preoperative durations for both genders. Although our study did not yield explanatory data, we hypothesize that this discrepancy may be attributed to inherent differences in extremity dimensions between genders.

Our findings underscore the importance of standardized surgical approaches and consistent follow-up protocols for elucidating factors associated with recurrence and outcomes. Notably, although several factors have been implicated in TGCT recurrence, including tumor size, invasion of adjacent structures, and incomplete resection (21), our study did not identify a significant association between gender or anatomical location and

recurrence. Furthermore, our investigation highlights the heterogeneity in TGCT presentation across different anatomical locations within the hand, emphasizing the need for tailored management strategies based on tumor localization. However, further studies with larger sample sizes are warranted to validate these findings and elucidate additional factors influencing TGCT recurrence and clinical outcomes.

Conclusion

Our comprehensive analysis of 95 cases of localized TGCTs spanning 12 years provides valuable insights into the demographic characteristics and clinicopathological features of this condition. Our study revealed a low recurrence rate of 4.21%, which is likely attributable to meticulous surgical techniques and the extensive experience of our surgical team. Although our findings corroborate previous literature regarding the anatomical distribution of TGCTs in the hand, with a predilection for the first two digits, we did not observe a significant association between tumor location and recurrence. In addition, while involvement of important structures such as neurovascular elements and joint capsules has been implicated in recurrence in some studies, our analysis did not reveal a statistically significant relationship. Interestingly, we observed a significant difference in tumor size based on gender, with male patients presenting with larger tumors than females, highlighting a potential area for further investigation regarding the underlying factors contributing to this disparity. Our study underscores the importance of standardized surgical approaches and consistent follow-up protocols in elucidating factors associated with TGCT recurrence and outcomes. However, further research with larger sample sizes is warranted to validate these findings and identify additional factors influencing TGCT recurrence and clinical outcomes. Ultimately, our study contributes to ongoing efforts to optimize management strategies for TGCTs and improve patient outcomes.

Ethics

Ethics Committee Approval: The research protocol receiving approval from an Institutional Review Board of University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital (ethics committee protocol number: 2023/09/13/056).

Informed Consent: N/A.

Authorship Contributions

Surgical and Medical Practices: M.U., Concept: M.U., Design: M.U., M.F.D., O.B., Data Collection or Processing: N.Y.E., Analysis or Interpretation: N.Y.E., Literature Search: N.Y.E., M.F.D., O.B., Writing: M.F.D., O.B.

Conflict of Interest: No conflict of interest was declared by the authors.

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ORIGINAL RESEARCH

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Analysis of the Knowledge Level of Surgical Residents Regarding the Preoperative Assessment of Adult Elective Non-cardiac Surgery Patients with Specific Clinical Conditions

Elektif Non-kardiyak Cerrahi Geçirecek Spesifik Klinik Durumlara Sahip Hastalarda Cerrahi Asistanlarının Preoperatif Değerlendirme Hakkındaki Bilgi Düzeyinin Ölçülmesi

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Abstract

Objective: We aimed to analyze the knowledge level of surgical residents regarding preoperative assessment and increase their collaboration with other teams in optimizing the general medical status of patients to reduce the duration of hospital stay and complication rates.

Method: Our study included 80 surgical residents. The 2018 update of the European Society of Anesthesiology (ESA) was used during the preparation of the survey questions. The questions were categorized on the basis of the specific clinical conditions and medications noted in the ESA guidelines. Answer choices were "correct", "wrong" or "no idea."

Results: Analysis of the distribution of the mean correct answer rates (%) revealed that the question regarding "herbal medications" led to the lowest correct answer (13.75%), whereas the category "bridging and anticoagulation" was associated with the highest (72.5%) correct answer. The total mean correct answer was calculated as 50.8%. There was no significant correlation between the residents' seniority level (i.e., postgraduate year) and their correct answer rates in the neurosurgery, general surgery, ear-nose-throat, and plastic surgery divisions. However, there were statistically significant differences in the ophthalmology, urology, orthopedic surgery, and obstetrics and gynecology divisions.

Öz

Amaç: Cerrahi asistanlarının ameliyat öncesi değerlendirme konusundaki bilgi düzeylerini analiz etmeyi ve hastaların genel tıbbi durumlarını optimize ederek hastanede kalış süresini ve komplikasyon oranlarını azaltmak için diğer ekiplerle iş birliklerini artırmayı amaçladık.

Yöntem: Çalışmamız 80 cerrahi asistanıyla gerçekleştirilmiştir. Anket sorularının hazırlanmasında Avrupa Anesteziyoloji Derneği'nin (ESA) 2018 güncellemesinden yararlanılmıştır. Sorular, ESA kılavuzunda belirtilen spesifik klinik durumlara ve ilaçlara göre kategorize edilmiştir. Cevap seçenekleri "doğru", "yanlış" veya "fikrim yok" şeklinde olmuştur.

Bulgular: Ortalama doğru cevap oranlarının (%) dağılımı incelendiğinde, en düşük doğru cevabın "bitkisel ilaçlar" ile ilgili soru (%13,75) olduğu, en yüksek doğru cevabın ise "köprüleme ve antikoagülasyon" kategorisiyle (%72,5) ilişkili olduğu görülmüştür. Toplam doğru cevap ortalaması %50,8 olarak hesaplanmıştır. Asistanların kıdem düzeyleri (lisans üstü yıl) ile beyin cerrahisi, genel cerrahi, kulak-burun-boğaz ve plastik cerrahi branşlarındaki doğru cevap oranları arasında anlamlı bir ilişki saptanmamıştır. Ancak göz hastalıkları, üroloji, ortopedi ile kadın hastalıkları ve doğum bölümleri arasında istatistiksel olarak anlamlı farklılıklar bulunmuştur.

***We regret to inform you that Nagihan Karahan MD, has passed away.**

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Abstract

Conclusion: The general medical status of patients should be optimized to reduce the risk of complications. To achieve this goal, surgical residents should collaborate with other teams at each perioperative stage. In addition, we suggest that the curriculum be reviewed to increase the knowledge level of surgical residents regarding preoperative care.

Keywords: Elective non-cardiac surgery, knowledge level of residents, pre-operative assessment

Öz

Sonuç: Komplikasyon riskini azaltmak için hastaların genel tıbbi durumu optimize edilmelidir. Bu hedefe ulaşmak için cerrahi asistanlarının her perioperatif aşamada diğer ekiplerle iş birliği yapması gereklidir. Çalışmanın sonuçları doğrultusunda; cerrahi asistanlarının ameliyat öncesi bakım konusunda bilgi düzeyinin artırılması amacıyla müfredatın gözden geçirilmesini öneriyoruz.

Anahtar kelimeler: Ameliyat öncesi değerlendirme, asistanların bilgi düzeyi, elektif kalp dışı cerrahi

Introduction

Today, anesthesiologists' preoperative assessment of patients is considered critical because of the comorbid diseases accompanying the patients' clinical conditions necessitating surgical treatment. Novel strategies and preparation methods have emerged in health systems with developing technology. The primary aim of preoperative anesthesia assessment is to optimize the patient's medical condition before surgery and anesthesia administration (1).

Preoperative anesthesia assessment is implemented after the patient is referred to the anesthesiologist. The American Society of Anesthesiologists (ASA) recommended that preoperative anesthesia assessment be performed before the day of surgery in patients with high risk, while it could be implemented on the morning of the day of surgery in other patient groups. Although there are no standardized preoperative anesthesia assessment criteria, determination of the specific clinical conditions of the patients, anesthesia management, and follow-up during recovery are the responsibilities of the anesthesiologist (2).

It was determined that a preoperative anesthesia assessment performed before the day of surgery in close collaboration with the surgeon reduced the risk of complications and duration of hospital and intensive care unit (ICU) stays, provided that the comorbid clinical conditions of the patients were optimized. Therefore, this approach leads to effective use of ICU resources. Besides, during the preoperative anesthesia assessment, the patient can be counseled by the anesthesiologist and surgeon regarding the surgical procedure, anesthesia, and perioperative analgesia. It has been suggested that this strategy could reduce the anxiety of the patients (3,4).

The knowledge level of surgery residents is essential for the initial assessment of surgery patients, management of their comorbidities, and intraoperative and postoperative medical treatments. Relevant cooperation can reduce the rates of perioperative complications and duration of hospital stay, lead to effective use of ICUs, and decrease treatment costs. In our study, we analyzed the knowledge level of surgery residents regarding preoperative anesthesia assessment.

Materials and Methods

This study was conducted as a prospective, observational, single-center study. This study was approved by the Non-Interventional Clinical Studies Ethical Council of the İzmir Katip Çelebi University Atatürk Training and Research Hospital (12.05.2020/692). Written informed consent was obtained from the surgical residents. A Likert-type survey, including 41 questions, was prepared and applied to the surgical residents. This questionnaire was prepared on the basis of the European Society of Anesthesiology (ESA) guideline for the preoperative evaluation of adults undergoing elective non-cardiac surgery, which was updated in 2018. The survey questions were categorized according to the specific clinical conditions and medications mentioned in the ESA guidelines. The answer choices were "correct", "wrong" and "no idea". Demographic data of the surgical residents, such as age, gender, specialties, and postgraduate years, were also recorded. Overall, 100 surgical residents were enrolled in this study.

Surgery residents under training in cardiovascular surgery, basic science, or medical specialties were not included in this survey study. In contrast, residents under training in a surgical residency training program in our hospital other than cardiovascular surgery were included. In total, residents from eight different surgical programs were enrolled in our study.

Statistical Analysis

Statistical analysis of the data was performed using IBM SPSS Statics Version 24 software. Pearson's chi-square and Fisher's Exact tests were used to compare the groups regarding categorical data. Continuous data were non-normally distributed; Kolmogorov-Smirnov ($p<0.05$)

and Mann-Whitney U tests were used for intergroup comparisons. The relationship between the postgraduate years of the residents and the number of correct answers to the specific questions was analyzed by Spearman rho correlation analysis. A p-value of 0.05 was considered significant.

Results

This study was conducted with surgery residents of eight different surgical residency programs. Overall, 80 residents were included.

Analysis of the demographic data revealed that 73 (91.3%) residents were aged between 26 and 35. Sixty-five (81.2%) respondents were male, while 15 (18.8%) were female. Most (n=20, 25%) of the residents were in postgraduate year 4 (Table 1).

Investigation of the categorical distribution (%) of the rate of correct answers to the questions on specific clinical conditions showed that the mean correct answer rate was lowest in the "herbal medications" (13.8%), "kidney diseases" (22.5%), and "anemia and preoperative blood-saving strategies" (25.6%) categories. On the other hand, the mean correct answer rates were highest in the "bridging and anticoagulation" (72.5%), neuromuscular diseases" (67.5%), and "coagulation disorders" (65.8%) categories (Table 2).

The correlation analysis between the rates of correct answers to the questions regarding specific clinical conditions and the surgical residents' postgraduate year (i.e., seniority level) revealed no significant correlation between these two parameters in neurosurgery, general surgery, ear-nose-throat (ENT) surgery, and plastic surgery programs (p>0.05) (Table 3).

On the other hand, a positive, perfect, and statistically significant correlation was found between the correct answer rates of the ophthalmology residents to the questions regarding "bridging and anticoagulation" and their seniority level (p>0.05).

Table 1. Distribution of the subjects based on demographic data

		n	%
Age	18-25	4	5.0
	26-35	73	9.3
	36-45	3	3.8
Gender	Male	65	81.3
	Female	15	18.8
Residency programme	Neurosurgery	11	13.8
	General surgery	15	18.8
	Opthalmology	5	6.3
	Obstetrics and gynecology	15	18.8
	ENT	7	8.8
	Orthopedic surgery	11	13.8
	Plastic surgery	7	8.8
	Urology	9	11.3
Postgraduate year	1	16	20.0
	2	19	23.8
	3	17	21.3
	4	20	25.0
	5	8	10.0

ENT: Ear, nose and throat surgery

Table 2. Distribution of the mean answer rates of the subjects to the questions regarding specific clinical conditions

Spesific clinical conditions	Mean	SD	Median	Min.	Max.
CVS diseases (7 questions)	61.59	20.39	57.1	0	100
Respiratory diseases and OSAS (3 questions)	53.76	22.83	66.7	0	100
Kidney diseases (2 questions)	22.50	30.71	0	0	100
Diabetes (2 questions)	40.00	24.39	50	0	100
Obesity (2 questions)	48.13	35.08	50	0	100
Coagulation disorders (3 questions)	65.84	29.05	66.7	0	100
Anemia and preoperative blood saving strategies (4 questions)	25.63	23.86	25	0	100
Geriatric patients (2 questions)	48.75	21.01	50	0	100
Neuromuscular diseases (3 questions)	67.52	20.53	66.7	0	100
Herbal medications (1 question)	13.75	34.65	0	0	100
Psychotropic medications (6 questions)	42.92	27.14	33.3	0	100
Bridging and anticoagulation (2 questions)	72.50	35.49	100	0	100
Correct answers (total) (37 questions)	50.84	14.92	50	19.4	102.8

SD: Standard deviation, CVS: Cardiovascular system, OSAS: Obstructive sleep apnea syndrome

Table 3. Correlation between the rate of correct answers to the questions regarding specific conditions and the surgical residents' seniority levels

		Neurosurgery	General surgery	Opth	Obs&Gyn	ENT	Orthopedic surgery	Plastic surgery	Urology
CVS diseases	r	0.371	0.260	0.763	0.552	0.404	0.296	-0.265	0.203
	p	0.261	0.349	0.133	**0.033**	0.369	0.376	0.566	0.600
Respiratory diseases and OSAS	r	-0.528	0.033	0.263	0.032	0.163	-0.451	-0.438	-0.101
	p	0.095	0.907	0.669	0.910	0.728	0.163	0.325	0.796
Kidney diseases	r	0.077	0.064	-0.115	0.642	-	-0.680	-0.535	-0.206
	p	0.822	0.821	0.854	**0.010**	-	**0.021**	0.216	0.595
Diabetes	r	-0.166	0.386	0.344	0.604	0.105	0.082	-0.663	-
	p	0.625	0.156	0.571	**0.017**	0.823	0.811	0.105	-
Obesity	r	0.599	-0.137	0.487	-0.438	0.000	-0.224	-0.384	0.772
	p	0.052	0.626	0.406	0.103	1.000	0.508	0.395	**0.015**
Coagulation disorders	r	-0.484	0.033	0.803	0.047	0.278	0.024	-0.407	0.642
	p	0.131	0.907	0.102	0.867	0.547	0.943	0.365	0.063
Anemia and preoperative blood saving strategies	r	-0.063	-0.116	0.158	0.474	0.297	-0.145	-0.642	-0.419
	p	0.854	0.680	0.800	0.074	0.518	0.670	0.120	0.262
Geriatric patients	r	-0.206	0.192	0.344	0.091	0.105	-0.131	0.642	-
	p	0.543	0.494	0.571	0.746	0.823	0.702	0.120	-
Neuromuscular diseases	r	-0.591	0.098	0.287	0.379	-0.010	-0.122	-	-0.303
	p	0.056	0.729	0.640	0.164	0.984	0.722	-	0.428
Herbal medications	r	-0.103	0.281	0.363	0.203	-	-0.256	-	-0.303
	p	0.763	0.310	0.548	0.467	-	0.448	-	0.428
Psychotropic medications	r	-0.377	0.302	0.553	0.140	0.481	-0.212	0.135	-0.681
	p	0.253	0.273	0.334	0.619	0.274	0.530	0.773	**0.044**
Bridging and anticoagulation	r	-0.051	0.383	0.892	-0.230	0.488	-0.414	0.000	-
	p	0.882	0.158	**0.042**	0.409	0.267	0.206	1.000	-
Correct answers (total)	r	-0.363	0.291	0.462	0.288	0.352	-0.329	-0.252	0.057
	p	0.272	0.293	0.434	0.298	0.439	0.324	0.585	0.885

Spearman Rho correlation. ENT: Ear, nose and throat surgery, CVS: Cardiovascular system, OSAS: Obstructive sleep apnea syndrome

There was a moderate positive correlation between the correct answer rate of the obstetrics and gynecology residents to the cardiovascular system (CVS) disease questions and their seniority levels and a positive, good-level, statistically significant correlation between the rate of correct answers to the "kidney diseases" and diabetes questions and their seniority levels (p>0.05).

There was a negative, good-level, and statistically significant correlation between the rate of correct answers of the orthopedic surgery residents to the "kidney diseases" questions and the residents' seniority levels (p>0.05). On the other hand, there was a positive, good-level correlation between the correct answer rates of the urology residents to the obesity questions, total correct answer rates, and these residents' seniority levels (p>0.05). Analysis of these residents' answers to the questions regarding psychotropic medications revealed a negative, good-level, and statistically significant correlation between the correct answer rates and the postgraduate year of the residents (p>0.05).

There was no statistically significant correlation between the rates of correct answers of the ophthalmology, obstetrics and gynecology, orthopedic surgery, and urology residents to the questions from other categories and the residents' seniority levels (p>0.05).

Discussion

There has yet to be a consensus regarding preoperative assessment standards, preoperative investigations, and their timing in patients undergoing elective non-cardiac surgery. In Turkey, the preoperative assessment guide prepared by tard (Turkish Society of Anesthesiology and

Reanimation) agrees with those of ASA and ESA. Although preoperative investigations target the best standard of care, their benefits are debatable in the setting of low-risk surgeries (2,5).

In our study, the analysis regarding the distribution (%) of the correct answers of the surgery residents to specific clinical conditions revealed that the correct answer rate was lowest in the "herbal medications" category (13.8%) and highest (72.5%) in the "bridging and anticoagulation" category. Furthermore, these rates were 22.5% in "kidney diseases", 25.6% in "anemia and blood-saving strategies", 48.1% in "obesity", 40% in "diabetes", 48.8% in "geriatrics" categories and 50.8% in total. Because the correct answer rates were low in questions related to vital topics, we suggest that surgical residents collaborate closely with the anesthesiology teams and other branches in the preoperative period.

The rate of surgical procedures is increasing in the geriatric patient population. Furthermore, this patient group has comorbidities and "polypharmacy" (i.e., the use of multiple medications). Thus, the risk of postoperative delirium and other complications is higher in these patients than in younger patients (6).

In our study, we found that the correct answer rate of the surgical residents to the questions about "geriatric patients" was 48.8%. This rate was lowest (40%) in the obstetrics and gynecology residents' group and highest (57%) in the plastic surgery residents' group. We suggest that the perioperative complication risk will be reduced if the surgical residents have more profound knowledge about the unique aspects of the geriatric patient population and geriatric physiopathology during preoperative patient management.

There is an approximately 50% risk of perioperative myocardial damage in patients undergoing major noncardiac surgery. In patients with cardiac risks, preoperative optimization of the general medical status and stabilization of the patient regarding comorbidities can improve the outcomes. On the other hand, the decision concerning the cessation of aspirin treatment should be made by an individualized approach considering the pros and cons for the patients based on ESA and European Society of Cardiology guidelines (7-9).

Our survey contained seven questions on CVS diseases with a 61.6% correct answer rate. The correct answer rate was highest (66.7%) for the urology residents and lowest (54.5%) for the orthopedic surgical residents. There was a positive, moderate level, and statistically significant correlation between the correct answer rates of the obstetrics and gynecology residents to the CVS disease questions and their seniority levels (i.e., post-graduate year) ($p>0.05$). We suggest that perioperative cardiac complication rates can be reduced if surgeons keep themselves updated regarding the most recent medical innovations and current practice guidelines.

A study by Mutter et al. (10) determined that the preoperative administration of continuous positive airway pressure led to a decrease in the rate of postoperative complications. Therefore, patients should be screened preoperatively for obstructive sleep apnea syndrome (OSAS) (10,11). Smoking cessation at least 4 weeks before surgery is critical for respiratory complications, wound healing, and wound infections (12,13). Because most patients are not referred to an anesthesiologist at that stage, surgeons should be aware of the importance of preoperative smoking cessation.

In our study, three questions were asked regarding OSAS and respiratory diseases. One question was asked regarding smoking. The correct answer rate was 53.76%. While the highest (60%) correct answer rate was detected in general surgery, ophthalmology residents had the lowest (46.7%) correct answer rate.

Preoperative cessation of anticoagulant medications or maintenance of anticoagulation at this stage is a critical topic, and several studies have been conducted on this subject. Yamamoto et al. (9) determined that patients who received dual antiplatelet treatment after coronary angiogram and underwent non-cardiac surgery had a higher risk of bleeding than those on a single antiplatelet drug.

Our survey had two questions regarding bridging and anticoagulation; the mean correct answer rate was 72.5%. While orthopedic surgery residents had the highest (86.4%) correct answer rate, plastic surgery and ophthalmology residents had the lowest (50%) correct answer rates.

In the study of Laflı Tunay (14), which analyzed the knowledge level and attitudes of family physicians regarding preoperative patient management, it was reported that relatively more comprehensive preoperative patient care protocols should be used in medical school curricula.

In our study, the mean correct answer rate of the eight surgical divisions was calculated as 50.8%. Therefore, we suggest that a more comprehensive preoperative patient management curriculum should be followed during surgical residency training to increase the surgical residents' knowledge levels.

Conclusion

Preoperative assessment of patients is vital for anesthesiologists, other medical doctors, and surgeons. We suggest that to decrease the rates of potential complications and optimize the preoperative general medical status of patients, surgical residents should be knowledgeable about preoperative patient care and collaborate closely with the anesthesia teams. In addition, the medical school and surgical residency training curricula should be revised to heighten their knowledge of preoperative patient management.

Information: This article has been produced from a medical specialty thesis written with the approval of the Non-Interventional Clinical Studies Ethical Council of the İzmir Katip Çelebi University Atatürk Training and Research Hospital (12.05.2020/692).

Ethics

Ethics Committee Approval: This study was conducted as a prospective, observational, single-center study. This study was approved by the Non-Interventional Clinical Studies Ethical Council of the İzmir Katip Çelebi University Atatürk Training and Research Hospital (12.05.2020/692).

Informed Consent: Written informed consent was obtained from the surgical residents.

Authorship Contributions

Surgical and Medical Practices: G.A., M.A., S.G., N.K., Concept: G.A., M.A., S.G., N.K., Design: G.A., M.A., S.G., N.K., Data Collection or Processing: G.A., M.A., S.G., N.K., Analysis or Interpretation: G.A., M.A., S.G., N.K., Literature Search: G.A., M.A., S.G., N.K., Writing: G.A., M.A., S.G., N.K.

Conflict of Interest: No conflict of interest was declared by the authors.

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ORIGINAL RESEARCH

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Evaluation of the Long Head of the Biceps Tendon Using Shear Wave Elastography and Superb Microvascular Imaging in Cases of Biceps Tendinopathy

Biseps Tendinopatisi Olgularında Biseps Tendonunun Uzun Başının Shear Wave Elastografi ve Süperb Mikrovasküler Görüntüleme Yöntemleri Kullanılarak Değerlendirilmesi

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Abstract

Objective: To evaluate biceps tendon long head (LHBT) tendinopathy cases using shear wave elastography (SWE) and superb microvascular imaging (SMI) methods, compare the findings with magnetic resonance imaging (MRI) findings, and make an early diagnosis of tendinopathy.

Method: Twenty patients diagnosed with LHBT tendinopathy on MRI and 20 healthy volunteers with normal LHBT on MRI were prospectively evaluated using the SWE and SMI methods. Quantitative measurements of LHBT hardness by SWE were performed in kilopascals (kPa). SMI values were determined using a rating system. A four-stage grading system was used as follows: grade 0 (no significant vascularity focus), grade 1 (1-2 focal vascularity focus), grade 2 (1 linear or more than 2 focal vascularity focus), and grade 3 (more than 1 linear vascularity focus).

Results: While the average SWE values for the biceps tendon with tendinopathy were measured as 38.715 and 37.685 kPa in the longitudinal and transverse planes, respectively, the average SWE values of the control group were measured as 19.385 and 18.41 kPa in the longitudinal and transverse planes, respectively. This shows that there is a statistically significant difference ($p<0.01$). In the evaluation performed using SMI, intratendinous grade 1, 2, or 3 flow was detected in all patients with tendinopathy. According to the ANOVA test, there was a statistically significant difference between the degree of vascularization determined by the SMI method and the average symptom onset in cases with

Öz

Amaç: Biseps tendon uzun başı (LHBT) tendinopatisi olgularını shear wave elastografi (SWE) ve süperb mikrovasküler görüntüleme (SMI) yöntemleriyle değerlendirmek, bulguları manyetik rezonans görüntüleme (MRG) bulgularıyla karşılaştırmak ve tendinopatinin erken tanısını koymaktır.

Yöntem: MRG'de LHBT tendinopatisi tanısı alan 20 hasta ve MRG'de LHBT'si normal olan 20 sağlıklı gönüllü SWE ve SMI yöntemleri kullanılarak prospektif olarak değerlendirildi. LHBT sertliğinin SWE ile kantitatif ölçümleri kilopaskal (kPa) cinsinden belirlendi. SMI değerleri bir derecelendirme sistemi kullanılarak belirlendi. Dört aşamalı bir derecelendirme sistemi şu şekilde kullanıldı: Derece 0 (önemli vaskülarite odağı yok), derece 1 (1-2 fokal vaskülarite odağı), derece 2 (1 doğrusal veya 2'den fazla fokal vaskülarite odağı), derece 3 (1'den fazla doğrusal vaskülarite odağı).

Bulgular: Tendinopatili biseps tendonunun ortalama SWE değerleri uzunlamasına ve enine düzlemde sırasıyla 38,715 kPa ve 37,685 kPa olarak ölçülürken, kontrol grubunun ortalama SWE değerleri uzunlamasına ve enine düzlemde 19,385 kPa ve 18,41 kPa olarak ölçüldü. Bu durum istatistiksel olarak anlamlı bir fark olduğunu göstermektedir ($p<0,01$). SMI ile yapılan değerlendirmede tendinopatili olguların tamamında tendinit içi derece 1, 2 veya 3 akım tespit edildi. ANOVA testine göre tendinopatili olgularda SMI yöntemiyle belirlenen vaskülarizasyon dereceleri ile

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Abstract

tendinopathy (p<0.001). No statistically significant correlation was found between symptom onset time and SWE values measured in the transverse and longitudinal planes.

Conclusion: The combined use of SMI and SWE in addition to conventional US can be useful diagnostic methods as easy and practical techniques in the evaluation of the tendon in cases with LHBT tendinopathy.

Keywords: Biceps tendinopathy, biceps tendon long head tendinopathy, shear wave elastography, superb microvascular imaging

Öz

semptom başlangıç ortalamaları arasında istatistiksel olarak anlamlı fark vardır (p<0,001). Semptomun başlangıç zamanı ile transvers ve longitüdinal düzlemde ölçülen SWE değerleri arasında istatistiksel olarak anlamlı bir ilişki bulunamadı.

Sonuç: LHBT tendinopatili olgularda tendonun değerlendirilmesinde konvansiyonel US'ye ek olarak SMI ve SWE'nin birlikte kullanımının kolay ve pratik teknikler olarak faydalı tanı yöntemleri olabileceğine inanıyoruz.

Anahtar kelimeler: Biseps tendinopatisi, biseps tendon uzun başı tendinopatisi, shear wave elastografi, süperb mikrovasküler görüntüleme

Introduction

Tendinopathy refers to pain that worsens with movement without tendon tear. The prevalence of tendinopathy is 2-5% (1). Although the risk of tendinopathy is high in active and sporty people, it is also common in inactive people. Biceps tendinopathy occurs as a result of tendon degeneration resulting from overhead movement or normal aging. Tendinopathy of the long head of the biceps tendon (LHBT) is often accompanied by rotator cuff tears or superior labrum anterior posterior lesions (2). Degeneration and repair processes that cause pain and swelling when exposed to forces such as tension, compression, and friction beyond the tendon's capacity play a role in its pathophysiology (3). Patients with LHBT tendinopathy report severe and throbbing pain in the anterior shoulder. Conventional ultrasonography (US) and magnetic resonance imaging (MRI) are diagnostic non-invasive imaging methods for LHBT tendinopathy. Conventional US has the advantages of being easily accessible and inexpensive compared with other imaging techniques. However, it has diagnostic limitations because it is user dependent and the echogenicity of the tendon and surrounding tissues is similar in cases of tendinosis. MRI is the gold standard non-invasive imaging method for the diagnosis of tendinosis (4).

Sonoelastography is a new US method that evaluates differences in tissue stiffness. Sonoelastography includes strain elastography and SWE. Strain elastography evaluates tissue tension by applying mechanical external pressure to the tissue. SWE is a method in which small displacements in the tissue are measured by applying a short-term (0.03-0.4 ms), high-power (frequency 2.67 MHz) acoustic driving force to the tissue with ultrasound probes (5). In healthy tendons, type 1 collagen fibers are responsible for the elasticity of the tissue. In patients with chronic tendinopathy, disorganization of type 1 collagen fibers in the tendon, deterioration in tissue organization, and scattered irregular proliferation of smaller collagen fibers occur. This causes thickening of the tendon, a decrease in energy storage capacity, and tendons exhibiting more tension for the same load. This results in an increase in tissue stiffness and a decrease in elasticity (3).

Neovascularization develops due to chronic degeneration in the tendon because of tendinopathy. Doppler US has been used to demonstrate neovascularization in pathological tendon. However, it has limitations such as angular dependence and inability to visualize small vessels. The SMI method is a technique that can show small-diameter slow-flow vessels (6). Thus, it has superiority over the Doppler US technique in showing neovascularization in the tendon.

SWE and SMI techniques have not yet been used in routine clinical practice. However, studies on these two methods have been conducted on the breast, testicles, lymph nodes, and thyroid (7). In addition, in recent years, it has been used as a new method to evaluate different conditions in the musculoskeletal system (8). There is no study in the literature that uses both the SWE and SMI methods in LHBT tendinopathies. The aim of our study was to compare the LHBT of the normal shoulder with the LHBT of the shoulder with tendinosis using these two methods and to verify it with MRI findings.

Materials and Methods

Ethics committee approval numbered 2019/184 was obtained from the Trakya University's Ethics Committee for our prospectively designed study.

We identified the cases who applied to our Trakya University Hospital with shoulder pain between June 2023 and September 2023 and subsequently requested MRI for further examination. We included patients with tendinosis

detected in MRI examinations in our study group and evaluated them using the SMI and SWE methods.

A total of 60 shoulder MRI examinations were examined, and 20 patients with LHBT tendinosis who met the criteria of our study and participated voluntarily and 20 control groups with normal shoulder MRI were included in our study. LHBT tendinosis and the control group were prospectively examined using SWE and SMI methods. The ethics committee and approval forms were obtained.

Patient Selection

Patients with acute trauma, ipsilateral shoulder surgery, LHBT tendon rupture, advanced rotator cuff arthropathy, adhesive capsulitis, and muscle disease were excluded from the study because subluxation and dislocation of the LHBT tendon would cause tension in the tendon. In addition, uncooperative cases that could not be examined by US and cases whose MRI did not have sufficient resolution and diagnostic quality were excluded from the study. In addition, five patients were excluded from the study because they were used for standardization during the learning phase of the US method.

MRI Technique

MRI was performed using a 1.5 Tesla MRI device (MAGNETOM Aera, Siemens Medical Systems, Enlargen, Germany) using a superficial shoulder coil. In the images; T1-weighted: T1-TSE (Turbo Spin-Echo) axial, T1-TSE oblique coronal (780/15; FOV 14 cm; slice thickness 3.5 mm; intersection range 0.4 mm; matrix 320×256), T2-weighted: T2-FFE (Fast Field Echo) axial, T2-TSE oblique sagittal, T2-weighted fat suppressed, T2-SPAIR (spectral attenuated inversion recovery) axial and oblique coronal (3400/50; FOV, 14 cm; diagonal) -slice thickness 3.5 cm; intersection gap 0.4 mm; matrix, 256×256) images were obtained.

All MRIs were independently evaluated by two radiologists experienced in musculoskeletal pathology, and cases interpreted as tendinosis were subsequently evaluated. Cases in which no tear was observed in the LHBT tendon on MRI and in which fluid, signal, and increased thickness were observed around the tendon were evaluated as tendinosis. LHBT thickness was measured in the transverse plane, 1-2 cm distal to the tendon insertion level.

SWE and SMI Techniques

All participants were evaluated using B-mode US, SWE, and SMI methods, and measurements were made using the linear probe (PVT-375BT, Canon Medical Systems, Otawara, Japan) of the high-frequency US device in our department.

Patients were informed in detail about the procedure to be performed and were asked to remain comfortable throughout the procedure. Afterwards, B-mode US, SWE, and SMI measurements of the patients; it was performed by two independent radiologists with 5 years of radiology experience. All measurements were performed with the participants sitting, arm neutral, forearm on the thigh, and hand in a supinated position (9). The linear probe was placed in the anterior shoulder, and LHBT was evaluated in the transverse and longitudinal planes of the bicipital groove. Tendon echogenicity, thickness, and fluid content in the tendon sheath were evaluated during B-mode US. Tendon thickness was measured in the transverse plane 2 cm distal to the insertion level of the LHBT. After B-mode US, measurements were made using the SWE and SMI methods. All measurements were performed in transverse and longitudinal planes. SWE and SMI measurements were performed separately by two radiologists and then decided by mutual consensus. During the SWE measurements, a 3 mm diameter ROI circle was placed, as shown in Figure 1. Measurements in the longitudinal plane were made 1-4 cm away from the proximal border of the bicipital groove (Figure 2). When measuring in the transverse plane, the place where the tendon was most prominent in the bicipital groove was used. The quantitative value for LHBT was obtained using at least three measurements, and the mean values were used for statistical analysis. A 3-mm diameter ROI circle was used to make standard measurements for all participants. All SWE measurements were calculated in kilopascals (kPa).

In the SMI evaluation, a grading system was used. A four-stage grading system was used as follows: grade 0 (no

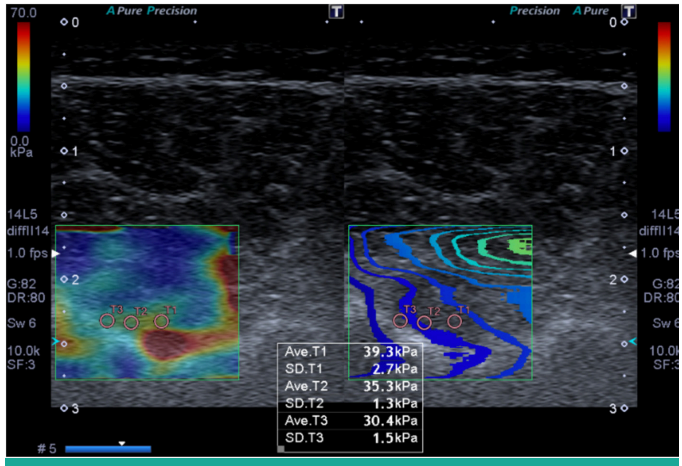

Figure 1. SWE measurement of the tendon of a patient with biceps tendinopathy in the transverse plane

SWE: Shear wave elastography

significant vascularity focus), grade 1 (1-2 focal vascularity focus), grade 2 (1 linear or more than 2 focal vascularity focus), and grade 3 (more than 1 linear vascularity focus). According to this grading system, biceps tendinopathy was considered positive in those with flow grades 1, 2, or 3 and negative in those with grade 0 (Figure 3).

The patients' images were transferred to our hospital's image storage (PACS) (Extremepacs, Ankara, Turkey) system. All measurements of the patients, and their characteristics, such as gender, age, biceps tendon thickness, and echogenicity, were recorded in the statistics program.

Statistical Analysis

Statistical Package for the Social Sciences (SPSS), version 16.0 (SPSS Inc, Chicago, IL) was used for all statistical analyses. Quantitative variables are expressed as mean ± standard deviation and categorical variables as frequencies or percentages. Baseline data were evaluated using the Kolmogorov-Smirnov test. Student's t-test was used for group comparisons of continuous variables with normal distribution; otherwise, Mann-Whitney U test was applied. Multiple subanalysis were performed. Pearson correlation analysis was used for the correlation quantitative values. The Wilcoxon signed rank test was used to evaluate differences in median SWE-SMI measurements between the biceps tendon with tendinopathy and the biceps tendon without tendinopathy. The area under the ROC curve and 95% confidence interval were calculated for each ROC curve analysis. For each statistical test, a p-value of 0.05 was considered significant.

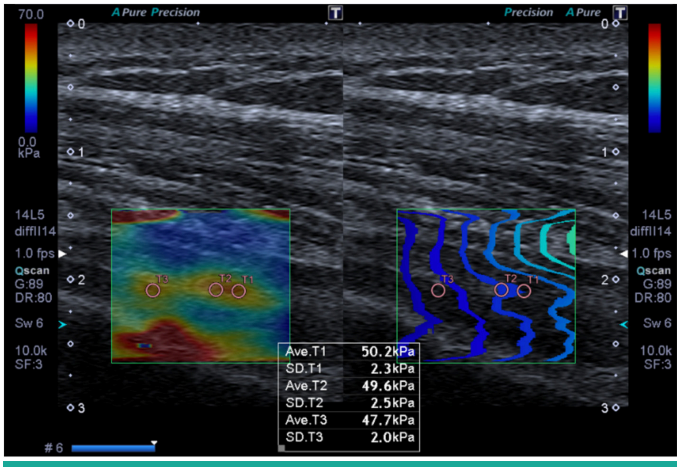

Figure 2. SWE measurement of the tendon of a patient with biceps tendinopathy in the longitudinal plane

SWE: Shear wave elastography

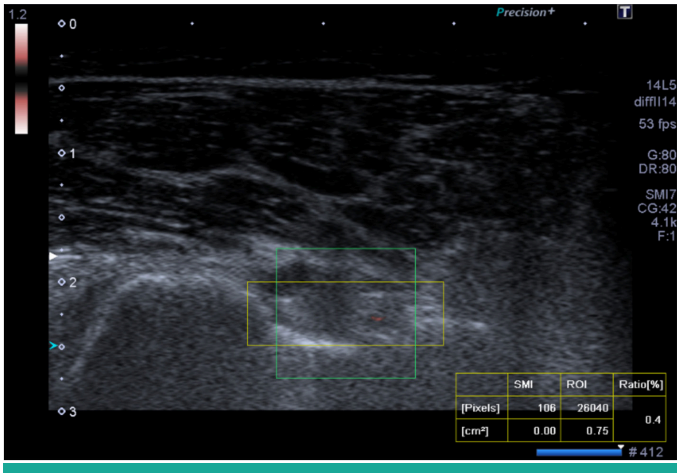

Figure 3. SMI measurement of the tendon of a patient with biceps tendinopathy in the transverse plane

SMI: Superb microvascular imaging

Results

The ages of the cases included in our study ranged between 25 and 83 years (mean: 50.05±16.15). Twenty patients, 12 (60%) females and 8 (47%) males, who met the inclusion criteria were included in the study group. Twenty cases were included in the control group; there were 10 (50%) women and 10 (50%) men.

Demographic data of all cases included in the study are shown in Table 1. The data of conventional US and MRI findings of all cases included in the study are shown in Table 2. Comparison of SWE mean values between the LHBT tendinopathy and control groups is shown in Table 3.

There was a statistically significant difference between the SWE values measured in the transverse plane of the cases with LHBT tendinopathy and the SWE values of the control group measured in the transverse plane. The mean SWE value of the control group (18.41) was significantly lower than the mean SWE value of the tendinopathy cases (37.685) (p<0.001).

There was a statistically significant difference between the SWE values measured in the longitudinal plane of the LHBT tendinopathy cases and the SWE values of the control group measured in the longitudinal plane. The mean SWE value of the control group (19.385) was significantly lower than the mean SWE value of the tendinopathy cases (38.715) (p<0.001).

Table 1. Demographic data of the patients and control group

	LHBT tendinopathy (n=20)	Control group (n=20)
Gender (F:M)	12:8	10:10
Age (years)	50.05±16.15	47.55±11.9

LHBT: Long head of the biceps tendon

There was a statistically significant difference between the thickness of the cases with LHBT tendinopathy measured on US and MRI and the thickness of the control group measured on US and MRI (p<0.001).

No significant difference was observed between the subcutaneous fat thickness between the skin and tendon of LHBT tendinopathy cases and the subcutaneous fat thickness of the control group (p=0.384).

The average symptom onset time of the patients before US was calculated as 59.25 (±40.4 to 78.0) days. There was no statistically significant correlation between the duration of symptom onset and SWE values measured in the transverse and longitudinal planes (p=0.836).

In the evaluation performed with SMI, intratendinous grade 1, 2, or 3 flow was detected in all cases with tendinopathy. Grade 1 flow was observed in 8 tendinopathy cases, grade 2 flow was observed in 4 cases, and grade 3 flow was observed in 8 cases. According to the ANOVA test, there was a statistically significant difference between the degree of vascularization determined by the SMI method and the average symptom onset in cases with tendinopathy (p<0.001). As the symptom duration increases, the average SMI value decreases; SMI values are high in the acute period (Table 4).

There was no statistically significant difference in terms of SMI values, tendon thickness, and tendon area averages in patients with tendinopathy (p=0.404).

Table 2. Tendon thickness measurements in US and MRI and tendon area measurements in US of patients and control groups

	LHBT tendinopathy (n=20)	Control group (n=20)	p-values
US tendon thickness (mm)	3.168 (±0.0549)	2.6645 (±0.395)	<0.001
MRI tendon thickness (mm)	3.1915 (±0.4216)	2.6755 (±0.4632)	<0.001
Tendon area (cm^2)	0.3085 (±0.045)	0.137 (±0.0249)	

LHBT: Long head of the biceps tendon, MRI: Magnetic resonance imaging, US: Ultrasonography

ROC analysis was performed between LHBT tendinopathy cases and the control group. SWE-kPa values measured in the transverse plane were found to have 85% sensitivity and 85% specificity with a cut-off value of 34.8. It was found to have 65% sensitivity and 70% specificity with a cut-off value of 38.1 in the longitudinal plane (p<0.001; p<0.002) [area under the curve (AUC): 0.823; AUC: 0.923, respectively] (Table 5, Figure 4).

Discussion

LHBT tendinopathy is a tendon injury that occurs as a result of chronic degeneration with an insidious onset, causing pain and functional impairment in the shoulder (3). Tendons experience cycles of damage and repair when they are exposed to more load than they can bear. Damage to type 1 collagen, the main structural component of the tendon, results in loss of normal fibril structure and disorganized fibrils. During the repair process, these damaged areas can heal with fibrosis. As a result, tendon elasticity decreases due to chronic degeneration and fibrosis (3,10,11). These structural changes in the tendon are evaluated on MRI as an increase in the tendon signal associated with the disruption of normal fibril structure. In US examination, there is an increase in tendon thickness, increased echogenicity, and fluid accumulation around the tendon. The SWE method can be used to evaluate the decrease in tendon elasticity, i.e., the increase in its stiffness. In addition, increased vascularity in the tendon is mentioned in tendinopathy cases (12). Studies have reported that the reason for this is that the release of angiogenic factors such as vascular endothelial growth factor increases in the tendon exposed to repetitive stress, resulting in local vascular hyperplasia (12). The Doppler US technique is not sufficient to show neovascularization in the tendon. The SMI method is a new US technique that can successfully demonstrate very small vessels and very low flow velocities.

Our study is usable in daily practice by comparing these current US methods with MRI findings in tendinosis cases.

Seo et al. (13) reported that sonoelastography showed a consistent correlation with conventional US in detecting intratendinous and peritendinous changes in LHBT in cases with symptoms related to biceps tendinopathy.

Table 3. SWE measurement averages of the patient and control groups in the transverse and longitudinal planes

	LHBT tendinopathy		Control group		p-values
	Transverse	Longitudinal	Transverse	Longitudinal	
SWE (kPa)	37.685 (±3.6985)	38.715 (±3.4581)	18.410 (±2.0504)	19.385 (±1.8633)	<0.001

SWE: Shear wave elastography, LHBT: Long head of the biceps tendon

Table 4. Comparison of symptom duration and SMI vascularization degree

SMI degree of vascularization	Symptom duration (days)
Degree 1	101.25 (±7.3649)
Degree 2	52.5 (±8.6603)
Degree 3	20.625 (±12.9387)

SMI: Superb microvascular imaging

Table 5. Receiver operating characteristic analysis results based on the evaluation of the SWE method for predicting biceps tendinopathy

	Cut-off	AUC	p	Sensitivity (%)	Specificity (%)
SWE transverse	>34.8	0.923	<0.02	85	85
SWE longitudinal	>38.1	0.823	<0.01	65	70

SWE: Shear wave elastography, AUC: Area under the curve

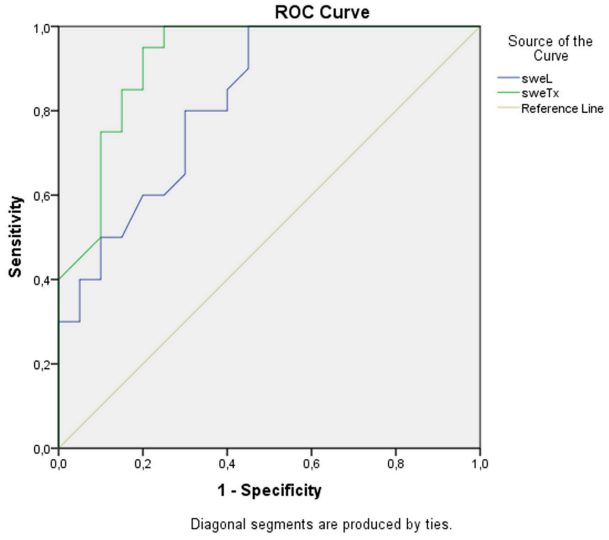

Figure 4. ROC curve
ROC: Receiver operating characteristic

Most studies on the elasticity properties of tendons are related to the Achilles tendon (14-16).

De Zordo et al. (14) compared conventional US and strain elastography methods in distinguishing the changes occurring in Achilles tendinopathy and found that strain elastography was more sensitive in detecting tendon changes before morphological changes appeared on US. In addition, softening of the tendon is observed in cases with tendinopathy compared with healthy volunteers, and they that this situation can be explained by very early changes in the tendon. In our study, we used the SWE method differently, and with this method, we observed an increase in SWE values in tendinopathy cases compared with the control group. We explained this situation with fibrosis that develops because of chronic degeneration in the tendon because of tendinopathy.

Klauser et al. (17) reported that adding sonoelastography findings to conventional US findings in the evaluation of lateral epicondylitis increased the sensitivity in detecting tendon pathology.

De Zordo et al. (18) evaluated the common extensor tendon using the sonoelastography method and stated that changes in the elasticity of the tendons of people with lateral epicondylitis symptoms may be useful in the diagnosis of lateral epicondylitis.

On the other hand, there is no difference between athletes and healthy volunteers in the sonoelastography evaluation of the patellar tendon (19). It has been reported that the sonoelastography technique has high applicability and reproducibility in the evaluation of healthy patellar tendon (20).

In a previous study, the accuracy of the sonoelastography technique in distinguishing tendon changes in patients with supraspinatus tendinopathy was compared with MRI and conventional US, and an excellent correlation was found between these modalities (21).

Many sonoelastography studies have been conducted on tendon pathologies in the evaluation of musculoskeletal system elastography, most of which are comparative studies with US, and most of them used the strain elastography technique. However, studies conducted using the SWE method are limited.

Unlike these studies in the literature, we used the SWE method and increased the reliability and specificity of our study by comparing it with MRI findings, which is a more objective modality.

In the study of Krepkin et al. (22), it was shown that there is a strong correlation between T2* values in MRI of the supraspinatus tendon and SWE values, and thus it was that it may allow a more quantitative evaluation of the rotator cuff tendons. Turkay et al. (23) evaluated tendons and found elasticity values to be lower in tenosynovitis cases than in healthy individuals. In our study, we observed higher elasticity values in patients with tendinopathy using the SWE method. We believed that this situation was related to the chronic process of the disease.

Color Doppler imaging methods have some limitations in showing small vessels and blood flow. It is insufficient to show thin vessels in the neovascularization that occurs in cases of tendinopathy. Zanetti et al. (24) reported that power Doppler imaging was insufficient to evaluate neovascularization in the tendon in cases with Achilles tendinopathy. To overcome these limitations, a new Doppler method, SMI, has been developed.

In the study by Arslan et al. (25), SMI was shown to have high accuracy rates in demonstrating common extensor tendon neovascularization in lateral epicondylosis cases, and a significant relationship was found between the SMI method and neovascularization and symptom duration. It has been reported that the degree of SMI decreases as the acute period progresses to the subacute period. In our study, an increase in vascularization was observed in patients with tendinopathy, and results consistent with the literature were found between symptom duration and vascularization. This may be due to inflammation in the acute phase.

Tendon studies with SMI are limited, and we believe that we have enriched our study by using the SMI method in addition to SWE. There are studies in the literature that use SWE and SMI methods together in the evaluation of breast, thyroid, lymph nodes, and testicles (26-28), but there is no study that we know of that uses the two methods in tendon evaluation.

According to our study, when we compared the results of tendinopathy cases evaluated with SMI and SWE methods with existing MRI findings, we obtained similar results, demonstrating the usability and reliability of these methods.

Study Limitations

There are a few limitations to our study. The first of these is the small number of patients, and we believe that more quantitative values can be found in large series studies. Our other limitation factors are that the majority of patients with biceps tendon pathology are associated with rotator cuff pathologies, and the effects of fluid in the tendon sheath on SWE and SMI results cannot be predicted. In addition, only MRI examination was used for comparison. More reliable information regarding the degree of tendinopathy can be provided with additional comprehensive studies using arthroscopy and histological findings.

Conclusion

The combined use of SMI and SWE in addition to conventional US may be useful diagnostic methods as easy and practical techniques in the evaluation of the tendon in cases with LHBT tendinopathy. SMI and SWE may be useful diagnostic tools for LHBT tendinopathy, considering their availability, cost-effectiveness, and patient preference compared with MRI.

Ethics

Ethics Committee Approval: Ethics committee approval numbered 2019/184 was obtained from the Trakya University's Ethics Committee for our prospectively designed study.

Informed Consent: Prospective study.

Authorship Contributions

Concept: F.U., G.B., B.G., C.B.A., F.E.U., Design: F.U., G.B., B.G., C.B.A., F.E.U., Data Collection or Processing: F.U., G.B., B.G., C.B.A., F.E.U., Analysis or Interpretation: F.U., G.B., B.G., C.B.A., F.E.U., Literature Search: F.U., G.B., B.G., C.B.A., F.E.U., Writing: F.U., G.B., B.G., C.B.A., F.E.U.

Conflict of Interest: No conflict of interest was declared by the authors.

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CASE REPORT

Bagcilar Med Bull 2024;9(2):135-138
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Long-term Complications of Female Genital Mutilation - Clitoral Epidermoid Inclusion Cyst

Kadın Genital Sünnetinin Uzun Vadeli Komplikasyonları - Klitoral Epidermoid İnklüzyon Kisti

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Abstract

This case study critically examines the long-term detrimental effects of female genital mutilation (FGM), specifically focusing on the development of clitoral epidermoid inclusion cysts. The study illuminates the often-overlooked post-mutilation complications that extend beyond immediate physical trauma, encompassing significant anatomical alterations with potential psychosocial implications. As a direct consequence of FGM, clitoral epidermoid inclusion cysts represent a physical manifestation of such prolonged complications, contributing to discomfort, potential sexual dysfunction, and an overall decline in quality of life. In an unusual case, a 38-year-old African woman presented with a painful clitoral tumor intermittently draining for three years. The study underscores the urgent need for comprehensive preventive measures, early diagnosis, and effective management strategies in affected populations to mitigate the enduring consequences of this harmful practice.

Keywords: Circumcision, clitoris, clitoromegaly, cyst, epidermal, inclusion

Öz

Bu olgu çalışması, kadın genital sünnetinin (FGM) uzun vadeli zararlı etkilerini kritik bir şekilde ele almakta, özellikle klitoral epidermoid inklüzyon kistlerinin gelişimine odaklanmaktadır. Çalışma, sadece anında fiziksel travmayı değil, önemli anatomik değişiklikleri ve potansiyel psikososyal sonuçları da kapsayan, genellikle göz ardı edilen sünnet sonrası komplikasyonları aydınlatmaktadır. FGM'nin doğrudan bir sonucu olarak, klitoral epidermoid inklüzyon kistleri, rahatsızlık, potansiyel cinsel işlev bozukluğu ve genel yaşam kalitesinde düşüşe katkıda bulunan uzun süreli komplikasyonların fiziksel bir göstergesidir. Olağandışı bir olguda, üç yıl boyunca aralıklarla drenaj yapan ağrılı klitoral bir tümör ile 38 yaşında bir Afrikalı kadın sunulmuştur. Çalışma, bu zararlı uygulamanın süregelen sonuçlarını hafifletmek için etkilenen popülasyonlarda kapsamlı önleyici tedbirler, erken tanı ve etkili yönetim stratejilerinin acilen gerekliliğini vurgulamaktadır.

Anahtar kelimeler: Epidermal, inklüzyon, kist, klitoris, klitoromegali, sünnet

Introduction

Around 125 million women and girls worldwide have undergone female genital mutilation (FGM)/mutilation (1), which is a common practice, particularly in African nations (2). Epidermal inclusion cysts are the procedure's most common complication (3). In comparison to the face, neck, and trunk, epidermal inclusion cysts are less frequently observed on the vulva, particularly the clitoris (4). Clitoral epidermal inclusion cysts are unusual and may develop on their own or as a result of trauma, particularly FGM, which can result in the implantation of the follicular epithelium into the dermis (5). Epidermoid clitoral cysts are frequently multicystic and develop gradually; once they reach a size of 5 to 6 cm, their pace of growth slows, but they continue to expand in a chronic environment (6). Their histopathology

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is distinct from others (7). In addition, even for big cystic lesions, entire mass excision yields better cosmetic and curative results (8).

Patient consent was duly obtained for the publication of this case report on the long-term complications of FGM, including clitoral epidermoid inclusion cysts.

Case Report

An African woman in her 38s arrived with a three-year-old painful, sporadic clitoral tumor. The mass brought on walking difficulties, dyspareunia, and embarrassment. She stated that this lesion had previously undergone three failed operations. The patient had two healthy pregnancies after undergoing Type 3 female genital circumcision at 13.

There were no complaints of episiotomies and no prior history of challenging vaginal birth. He did not have a history of illness or surgery, and he did not usually take any drugs. The patient stated that the tumor naturally subsided six months before his appointment, that the cyst was later medically evacuated, and that it recurred three months ago. The patient's discomfort has diminished since the incision and drainage, but she remains in need of diclofenac A 3x4 cm uncomfortably fluctuating cystic tumor was felt in the patient's clitoral region during a physical examination (Figure 1).

There were no signs of illness, a high fever, or redness on the patient. Surgery was performed on the patient after a soft tissue mass was discovered. A soft, yellowish lump that was easily removed after surgery and originated in the clitoral region was found (Figure 2).

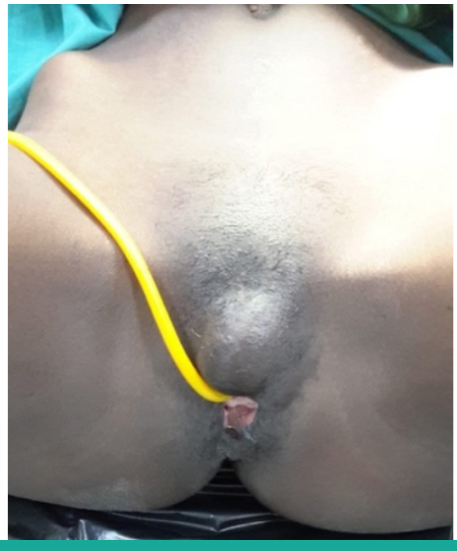

Figure 1. Preoperative inspection clitoral mass

A benign epithelial cyst was identified as the object that had been frozen. There were no signs of malignancy or teratomatous characteristics, such as skin adnexal structures.

A benign squamous mucosa with submucosal edema, chronic inflammation, fibrosis, and mild vascular congestion was found upon histopathological analysis of a paraffin incision (Figure 3).

The patient's surgical procedure was simple, and she was discharged from the hospital with no lasting effects. After excision, eighteen months later, there was no sign of recurrence.

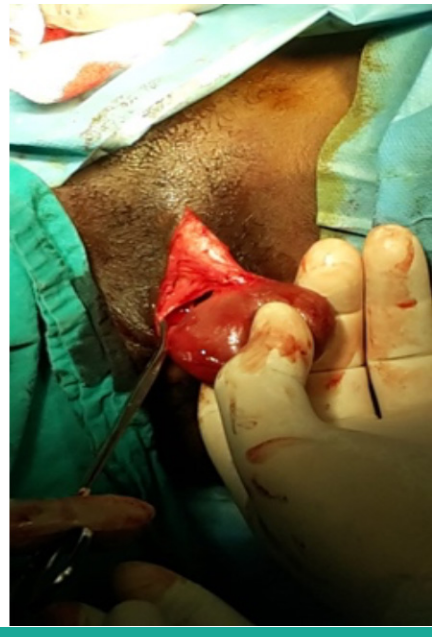

Figure 2. Surgical excision of the clitoral epidermal inclusion cyst

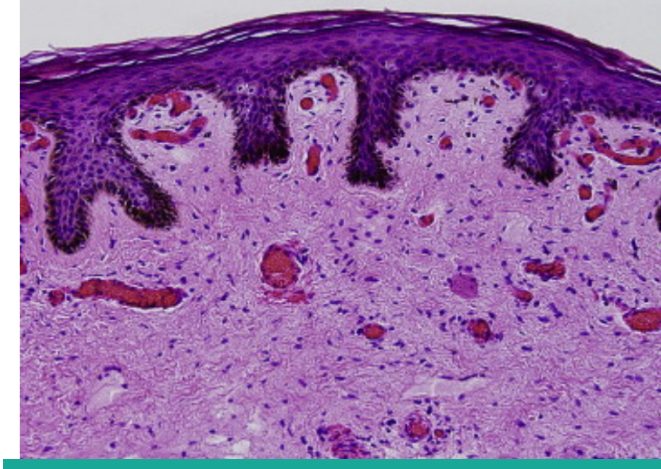

Figure 3. Paraffin block image of inclusion cyst

Discussion

In the shadow of the external genital region, there are pathological variations originating from adjacent anatomical structures (9), A clitoral cyst is one of these, and this case embodies an exceptional and infrequent occurrence. Existing literature contains many case reports concerning clitoral epidermoid inclusion cysts. However, most of these instances typically occur secondary to aesthetic interventions and traumas or are congenital cysts capable of imitating clitoromegaly, rendering the present case distinctively rare (10).

Epidermal or epidermoid cysts, also known as sebaceous cysts, are keratin-filled, subcutaneous cysts originating from hair follicles. These cysts, the most frequently observed type in the clitoris, are encased in epithelial cells and filled with keratin produced by these cells (11). Documentation exists linking these cysts with female genital incision, often referred to as circumcision. Despite their ordinary appearance on the vulva, they typically localize on the labia majora (12). Ritual circumcision in African children and women has led to a notable prevalence of clitoral epidermoid inclusion cysts due to vulvar trauma (13). There have also been rare reports of epidermoid cysts of the clitoris in white-skinned children and women with no history of vulvar trauma.

A singular documented series exists where 32 patients developed cases secondary to FGM. In this series, the mean cyst diameter observed was 4.2±2 cm, and the mean interval from FGM to hospital admission was 5±4 years. Our patient was found to be compatible with the mentioned series.

Enucleation or marsupialization of the cyst and its capsule is typically the treatment of choice. It remains paramount, however, to avoid any trauma to the urethral orifice and surrounding vulvar tissues during this procedure (14). It's equally important to locate and manage bleeding points within the cyst bed, to secure any surplus tissue flap during the excision, and to close the wound effectively, obliterating any dead space (15). Although the primary motivation for performing surgery on a clitoral inclusion cyst is often cosmetic, there are documented cases where large cysts have contributed to sexual difficulties leading to divorce (16).

In 2015, Vella et al. (17) published a review of the effects of FGM on the genitourinary system. Numerous studies have shown that surgical intervention is crucial in the care of FGM victims. The goal is to provide women the chance to enhance their sexuality while restoring normal anatomy. According to the same study (18), reconstructive surgery performed after FGM was associated with less pain and more recovered pleasure. The results from the one-year follow-up are encouraging. The majority of patients actively report an improvement in their sexual lives, and they note no change or, at the very least, no worsening of pain.

Conclusion

This case study focused on the long-term complications of FGM, specifically a clitoral epidermoid inclusion cyst, illuminates the severe physical, psychological, and sexual consequences of this harmful practice. The delayed diagnosis and treatment of this patient due to a lack of awareness about FGM-associated complications among healthcare providers emphasize the need for improved training in this area. This study also emphasizes the importance of considering the potential negative impacts on women's health when planning treatments. Although satisfactory outcomes were achieved post-treatment in this case, it underscores the need for careful planning and consideration to mitigate harmful health effects for women.

Ethics

Informed Consent: Patient consent was duly obtained for the publication of this case report on the long-term complications of FGM, including clitoral epidermoid inclusion cysts.

Authorship Contributions

Concept: M.C.D., H.A., Design: M.C.D., H.A., Data Collection or Processing: M.C.D., H.A., Analysis or Interpretation: M.C.D., H.A., Drafting Manuscript: B.G., S.E., Critical Revision of Manuscript: B.G., W.A., Technical or Material Support: W.A., S.E., Supervision: M.C.D., B.G., H.A., Final Approval and Accountability: W.A., S.E., Writing: H.A.

Conflict of Interest: No conflict of interest was declared by the authors.

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CASE REPORT

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Uterine Rupture: Fifteen Weeks of Non-communicating Uterine Horn Pregnancy

Uterin Rüptür: On Beş Haftalık Rüptüre Non-komünikan Rudimenter Horn Gebelik

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Abstract

We evaluated the management of a ruptured non-communicated rudimentary horn pregnancy at the 15th gestational week. A 22-year-old multigravida who was detected to have a 15-week pregnancy according to her last menstrual period was admitted to our clinic with abdominal pain. As the uterine cavity was imaged in 30 mm on transvaginal ultrasonography and front of the uterus 15-week-old fetus without cardiac activity, emergency laparotomy was performed with the possible diagnosis of uterine rupture. Diagnosis of rudimentary uterine horn pregnancy is challenging; thus, it can be encountered with the clinical picture of uterine rupture in later weeks of pregnancy. The most appropriate treatment in such patients is excision of the uterine horn.

Keywords: Müllerian ducts, pelvic pain, uterine rupture

Öz

Rüptüre olmuş 15 hafta non-kominike rudimenter uterin horn gebeliğin takip ve tedavisinde izlenmesi gereken yolu değerlendirdik. Yirmi iki yaşında gravida üç bir normal doğum bir abortusu olan son adet tarihine göre 15 hafta 4 günlük gebeliği olduğu tespit edilen hasta, kliniğimize karın ağrısı tablosu ile geldi. Transvajinal ultrasonda uterin kavitenin 30 mm düzensiz olması ve uterus önünde 12+5 hafta ölçülerinde kalp atışı olmayan fetüs tespit edilmesi üzerine uterin rüptür düşünülerek acil laparotomi yapıldı. Rudimenter horn gebeliğin tanısı koymak zordur. Bu nedenle ilerleyen gebelik haftalarında karşımıza rüptür ile gelebilir. Böyle bir hastada en uygun yaklaşım non-komunike uterin hornu eksize etmektir.

Anahtar kelimeler: Müllerian kanallar, pelvik ağrı, uterin rüptür

Introduction

Müllerian agenesis or hypoplasia can lead to variable uterine development and congenital absence of the vagina, known as Mayer-Rokitansky-Küster-Hauser syndrome. The resulting uterus can be a lateral hemi-uterus, uterine horns (e.g., unicornuate uterus), or a midline uterus without a cervix (it may most commonly fail to develop).

Lateral fusion defects lead to the development of symmetric or asymmetric organs (e.g., bicornuate uterus, uterus didelphys). Vertical fusion defects result in transverse vaginal septum, segmental vaginal agenesis, and/or cervical agenesis or dysgenesis (1,2).

Non-pregnant women present with symptoms such as hematometra, hematocolpos, retrograde menstruation, and endometriosis, causing pelvic pain. In pregnant patients, it manifests with symptoms such as recurrent miscarriages, preterm birth, intrauterine growth restriction, cervical insufficiency, fetal malpresentation, and rupture of the rudimentary horn (3,4).

Clinically, uterine rupture often presents as an acute abdominal emergency with intra-abdominal hemorrhage. Uterine rupture is an obstetric emergency that leads to maternal and fetal mortality and morbidity (5). Most reported cases in the literature are associated with scarred

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uterine rupture (6). Other predisposing factors, as in our case, include uterine anomalies. In this study, we identified a ruptured non-communicating rudimentary horn in a 16-week multigravida with a pre-diagnosis of uterine rupture. The thin myometrial layer in the rudimentary horn, as in this case, increases the likelihood of rupture.

Case Report

A 22-year-old patient with a history of one normal delivery and one abortion at 15 weeks presented to our clinic with widespread abdominal pain. Pelvic examination revealed cervical tenderness. Abdominal examination revealed signs of guarding and rebound tenderness. Arterial blood pressure was measured at 70/50 mmHg, and the pulse rate was 140 beats/min. Transvaginal ultrasound showed widespread free fluid in the pouch of Douglas, a 30-mm-thick fluid collection in the endometrium, and a fetus without cardiac activity at 12 weeks and 5 days in the anterior part of the uterus. Abdominal ultrasound revealed widespread free fluid in the liver and spleen. The preoperative hemoglobin level was measured at 6.5 g/dL. The patient underwent emergency laparotomy with a pre-diagnosis of uterine rupture. A midline incision was made to enter the abdomen. Rupture was observed in the right cornua region (Figure 1). Fetal observation was made in the abdominal cavity (Figure 2). Placental fragments were observed in the cornua (Figure 3) and excised. Approximately 3000 cc of hemorrhagic fluid was aspirated from the abdomen. The uterus, both ovaries, and fallopian tubes were intact. A 200-g dead fetus and placenta were removed from the abdomen. After hemostasis was achieved, the uterine horn was excised. The abdomen was closed. Subsequently, proper endometrial curettage was performed using a number 10 Karman cannula. After achieving hemostasis, the operation was concluded.

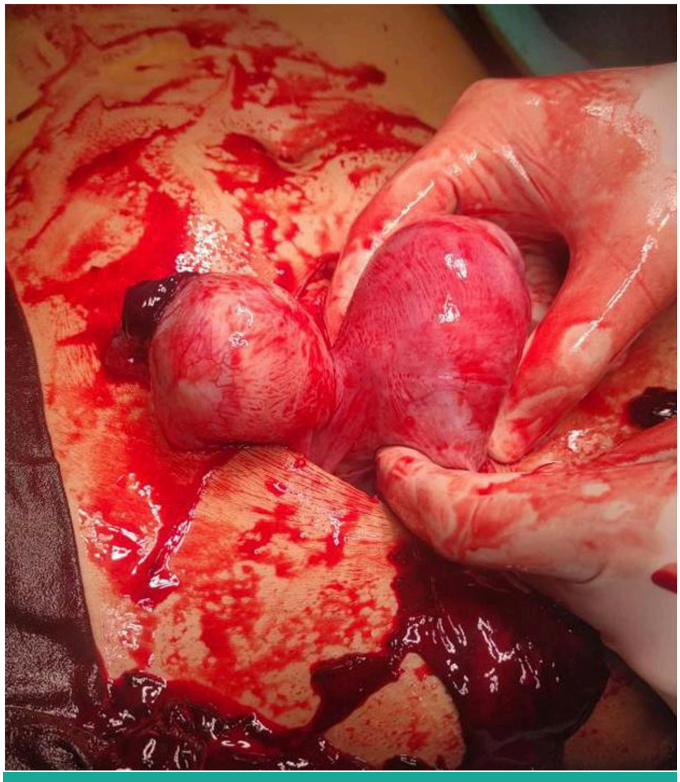

Figure 1. Ruptured uterine horn

Discussion

Müllerian agenesis/hypoplasia can lead to the development of congenital anomalies in the uterus, hymen, or vagina (e.g., unicornuate uterus), whereas fusion defects can result in the formation of uterus didelphys, bicornuate uterus, and/or vaginal septum. Additionally, in patients with Müllerian anomalies, 20% to 30% of them have kidney anomalies (7). These conditions commonly lead to gynecological complaints such as dysmenorrhea, dyspareunia, endometriosis, and infertility. Hematometra can develop in a rudimentary horn, which can be mistaken for a pelvic mass. Endometriosis can occur because of retrograde

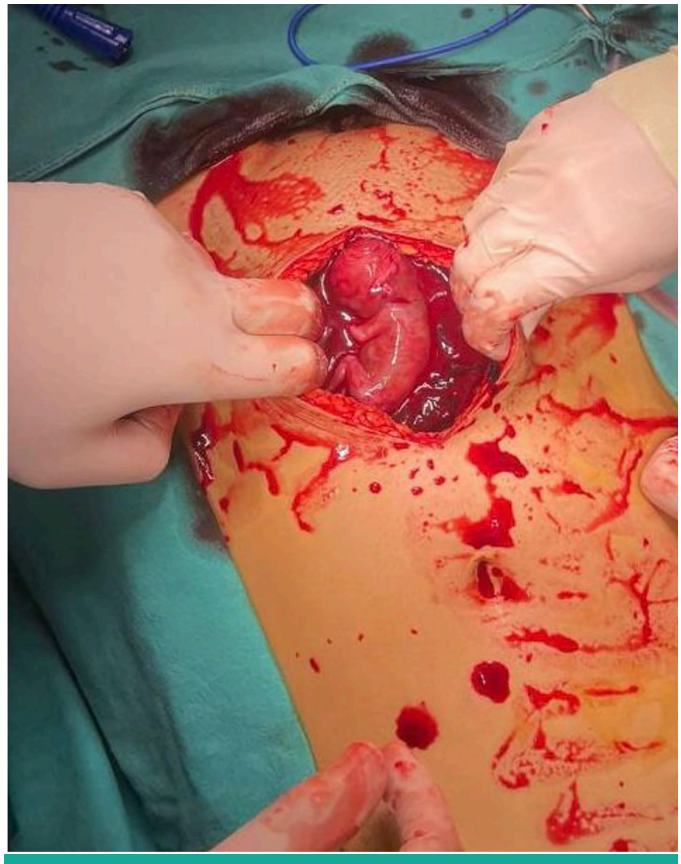

Figure 2. Fetus in the abdominal cavity

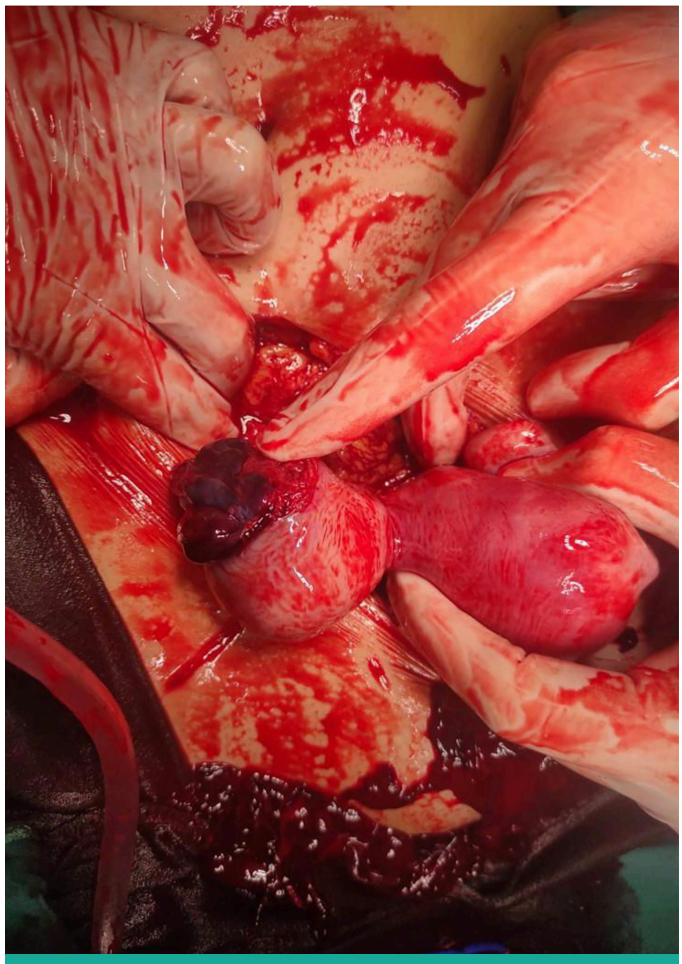

Figure 3. Right cornual region ruptured

menstruation. Patients with extensive endometriosis may present with infertility. In pregnant women, symptoms may include hypertension, recurrent miscarriages, preterm birth, postpartum bleeding, intrauterine growth restriction, fetal malpresentation, cervical insufficiency, placental invasion abnormalities, and uterine rupture. The vaginal septum can be a reason for cesarean section. Postpartum bleeding can occur because of placental attachment to the accessory part of the uterus. Pregnancy-induced hypertension has been associated with concomitant congenital renal anomalies (8).

The formation of non-communicating rudimentary horn pregnancies remains a subject of debate. Sperm migrate to the rudimentary horn through transperitoneal migration. This condition is associated with spontaneous abortion, preterm birth, intrauterine growth restriction, intraperitoneal hemorrhage, and uterine rupture. Because the myometrial layer is thin in the rudimentary horn, the risk of uterine rupture increases as the gestational weeks progress. Typically, uterine horn pregnancies present with rupture in the second trimester. Rare cases of term horn pregnancies have also been reported.

In non-communicating uterine horn pregnancies, high alpha-fetoprotein levels and abnormal uterine artery Doppler indices on ultrasonographic examination during second trimester screening have been reported (9).

In early-week ultrasonographic examinations, two separate endometrial linings were observed within two adjacent masses. However, as pregnancy progresses, the growth of the uterus carrying the fetus will obscure the other uterus, making the diagnosis more challenging. In this study, early diagnosis was not possible because of the absence of antenatal follow-up. Rudimentary horn excision was performed in our patient with fertility expectations. In the future, if pregnancy is not desired, hysterectomy can be performed to eliminate the risk of ectopic pregnancy. For patients with no fertility expectations who wish to menstruate, excision of the rudimentary horn with tubal ligation is a treatment option. Follow-up of the patient is necessary in the advanced stages for early detection of implantation in early pregnancy. In addition, precautions should be taken to reduce the risk of premature birth.

In conclusion, in rudimentary horn pregnancies, clinical suspicion, early diagnosis, and timely laparotomy can reduce maternal and perinatal mortality and morbidity. However, in recent years, a conservative approach has been advocated in well-informed, highly selective cases with sufficient myometrial thickness (10).

Ethics

Informed Consent: The patient's consent was obtained for this case report.

Authorship Contributions

Concept: T.K., S.N.S., Design: T.K., S.N.S., Data Collection or Processing: Ö.F.B., S.N.S., Analysis or Interpretation: Ö.F.B., S.N.S., Drafting Manuscript: Ö.F.B., S.N.S., Critical Revision of Manuscript: T.K., H.G., Final Approval and Accountability: T.K., H.G., Technical and Material Support: T.K., H.G., Supervision: H.G., Writing: Ö.F.B.

Conflict of Interest: No conflict of interest was declared by the authors.

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CASE REPORT

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Anesthesia Management in a Patient Diagnosed with Brugada Syndrome

Brugada Sendromu Tanılı Hastada Anestezi Yönetimi

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Abstract

Brugada syndrome (BrS) is a rare yet serious condition that can lead to death if not properly managed. Consequently, anesthesiologists must exercise special caution during the perioperative period. This report shares our experience with a patient diagnosed with type 3 BrS. We managed the intraoperative anesthesia in a 27-year-old patient scheduled for elective lumbar discectomy surgery. The patient had no additional comorbidities apart from BrS. After making the necessary preparations, the patient underwent surgery. Throughout the operation, the patient's hemodynamics remained stable. During the postoperative follow-up in the coronary intensive care unit, the patient reported experiencing chest pain and palpitations. However, no arrhythmia was detected, except for tachycardia. The patient was discharged after 48 h once clinical stability was achieved. In contrast to our case, patients who exhibit symptoms such as syncope, palpitations, and a family history indicative of cardiac diseases but have not been diagnosed with BrS should be thoroughly evaluated. It is crucial to ensure appropriate physiological and pharmacological conditions for these patients.

Keywords: Anesthesia, arrhythmia, Brugada syndrome

Öz

Brugada sendromu (BrS) nadir görülen ancak gözden kaçması durumunda ölümle sonuçlanabilecek ciddi bir hastalıktır. Bu nedenle anestezistlerin perioperatif özellikle dikkat etmesi gerekir. Bu raporumuzda tip 3 BrS tanılı hastayla ilgili deneyimimizi paylaşmayı amaçladık. Yirmi yedi yaşında elektif lomber diskektomi cerrahisi planlanan, BrS dışında ek özelliği olmayan hastanın intraoperatif anestezi yönetimi rapor edildi. Gerekli hazırlıklar yapılarak hasta operasyona alındı. İntraoperatif hemodinami stabil seyretti. Postoperatif koroner yoğun bakım ünitesinde takibi sırasında hastada göğüs ağrısı ve çarpıntı şikayeti meydana geldi. Taşikardi dışında aritmi saptanmadı. Kırk sekiz saat sonra klinik stabilite ile taburcu edildi. Olgumuzdan farklı olarak BrS tanısı olmayan ama kardiyak hastalıkları işaret eden aile öyküsü ve senkop, çarpıntı gibi semptomları olan hastalar dikkatlice sorgulanmalıdır. Bu hastalar için fizyolojik ve farmakolojik uygun şartlar sağlanmalıdır.

Anahtar kelimeler: Anestezi, aritmi, Brugada sendromu

Introduction

Brugada syndrome (BrS), first described by the Brugada and Brugada (1) brothers in 1992, is a rare condition that can lead to malignant arrhythmias and sudden cardiac death due to ion channel disorders associated with the transmission of electrical impulses in the heart. Anesthesiologists should be particularly mindful of this condition. It is characterized by autosomal dominant genetic transmission, primarily as sodium canalopathy due to *SCN5A* gene mutation. However, numerous gene mutations involving potassium and calcium channels have also been identified.

Electrocardiography (ECG) findings typically show ST segment elevation in the right precordial leads, independent of electrolyte disturbance, heart disease, or cardiac ischemia. However, these findings can vary depending on the time and conditions. Although BrS can be detected in all age groups, from early infancy to advanced age, it is most prevalent in the 20-40 age range, with a higher incidence in men (2).

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The only effective prophylactic treatment for these patients is an implantable defibrillator (ICD). However, it is recommended only for high-risk patients, such as survivors of cardiac arrest, those with a history of syncope caused by ventricular arrhythmias, or those who develop ventricular arrhythmias during a provocation test.

In this article, our aim is to share our experience with a patient diagnosed with type 3 BrS who exhibited minimal changes in ECG but could be overlooked during pre-operative evaluation.

Case Report

A 27-year-old male patient diagnosed with BrS was admitted to our hospital for elective L5-S1 discectomy. In his medical history, the patient presented to the neurology clinic in 2016 with complaints of headache, intermittent dizziness, and palpitations. After a normal neurological examination and detection of changes in his initial ECG, he was referred to the cardiology clinic where BrS was diagnosed. Since then, the patient has undergone regular check-ups every six months. His follow-up frequency increased to every two months after he experienced syncope for the first time in his life and was brought to the emergency department. A genetic test revealed a negative *SCN5A* gene mutation and a positive lipoprotein A gene mutation. He had undergone an uneventful appendectomy at the age of 12 years. His family history included heart failure in his father and arrhythmia in his sister. Laboratory examination showed normal complete blood count and electrolyte levels. The ECG showed normal sinus rhythm with no pathology detected other than T negativity in lead V1 (Figure 1). Echocardiography findings were normal.

Informed consent was obtained from the patient. An external defibrillator was kept open and ready in the operating room. Standard monitoring was applied. The patient's heart rate was 71 beats/min, non-invasive blood pressure was 108/66 mmHg, and peripheral SpO_2 was 99%. An intravenous route was established. The following preoxygenation, general anesthesia was induced with 7 mg/kg thiopental, 1 mcg/kg fentanyl, and 0.6 mg/kg rocuronium. The patient was intubated with a number 7.5 endotracheal tube. Maintenance of anesthesia was achieved with 6% desflurane, 50-50% air- O_2, and remifentanil infusion. Rocuronium (10 mg) was also administered every 30 min in the prone position. For postoperative analgesia, intravenous 0.5 mg/kg tramadol was administered. At the end of the surgery, 3 mg/kg sugammadex was administered to reverse the neuromuscular blockade. The operation proceeded smoothly, with stable vital signs, and lasted 130 min. The patient with regular and adequate spontaneous respiration was extubate. He was transferred to the cardiology intensive care unit for postoperative follow-up. There was no significant change in the postoperative ECG (Figure 2). During follow-up, the patient reported chest pain and nocturnal palpitations. Except for sinus tachycardia (max 122 beats/min), no arrhythmia was detected. The patient was re-evaluated by cardiologists before discharge. No findings were found in favor of ischemia or acute myocardial infarction. The patient was transferred to the Neurosurgery clinic at the end of 24 h. The follow-up period was completed to 48 h. He was discharged with clinical stability.

Discussion

The adult advanced life support guideline, published by the International Consensus on Cardiopulmonary Resuscitation in 2020, emphasizes the importance of predicting and preventing death due to sudden cardiac arrest, particularly in young adults. It urges serious consideration of the existence of misinterpreted and underestimated symptoms. In particular, it recommends

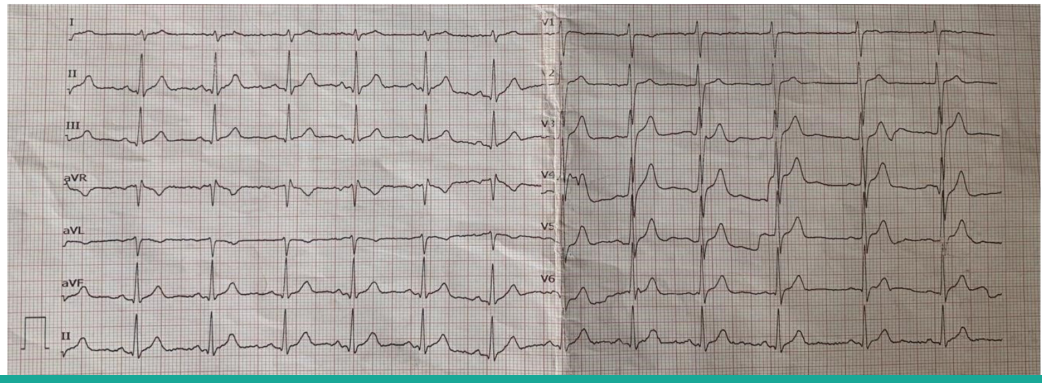

Figure 1. Preoperative electrocardiogram of the patient with Brugada syndrome

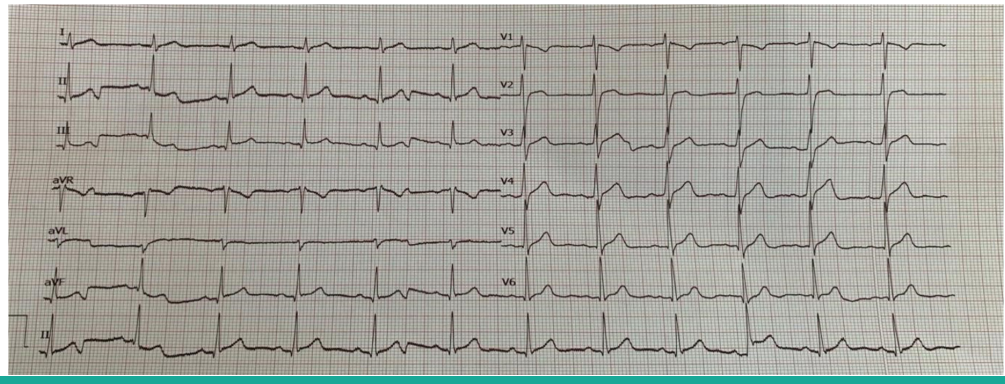

Figure 2. Postoperative control electrocardiogram of the patient with Brugada syndrome

thorough investigation of the causes of syncope (3). Similarly, the 2021 guideline of the European Resuscitation Council lists BrS among the electrical causes of sudden cardiac death, stating that it is often associated with sudden cardiac death in young people (4).

BrS, diagnosed in our patient, is identified as one of the leading causes of sudden cardiac arrest in individuals under the age of 40 years. It may exhibit autosomal dominant inheritance, but 60% of patients do not have an affected family member. Other risk factors include male sex, race (more common in Asians than other races), electrolyte disturbances, certain medications (www.Brugadadrugs.org.), fever, and use of alcohol and cocaine (2). Unpredictable problems and malignant arrhythmias that may occur during anesthesia management due to anesthetic drugs can trigger arrhythmias. Because we only have cases and case series in the literature, an ideal anesthesia management strategy for BrS has not yet been clarified. There is no definite recommendation for general or regional anesthesia in these patients; both can be preferred. In our patient, electrolytes such as sodium, potassium, and magnesium, which may aggravate the situation, were at normal levels. A cardiology opinion was obtained, and our patient was operated on under appropriate conditions. We planned general anesthesia.

High-dose use of propofol, known to be proarrhythmogenic, is one of the drugs that should be used with caution because it causes Brugada-like changes in ECG (5). However, there are also cases arguing that the use of a single dose in induction is safe (6,7). Because Brugada-like ECG findings have not been detected with thiopental to date, many studies have reported that it can be safely used (8,9). Therefore, we preferred thiopental for induction. From the data obtained, benzodiazepines can be used safely (7,10), while ketamine is among the drugs that should be avoided (5,11). We used fentanyl for induction and remifentanil for maintenance because there are publications indicating that these drugs can be safely used and no complications have developed (9). Although all volatile anesthetics are known to cause QT interval prolongation, it has been suggested that the use of isoflurane, sevoflurane, and desflurane does not produce cardiac arrhythmogenic effects (6). Because of the low blood gas solubility, we preferred desflurane as a maintenance anesthetic. Because there were no case series with any complications for rocuronium, we used it safely (8). We administered low-dose tramadol for postoperative analgesia. Tramadol is indicated among the drugs that should be used with caution (5,11). There is a report showing Brugada-like changes in ECG because of high-dose tramadol administration (12). The clinical risk of this drug at therapeutic doses is unknown, and stronger evidence is needed to contraindicate its use. We preferred sugammadex to reverse the neuromuscular block while the anesthesia was terminated because it is an antidote of rocuronium, it does not have any mechanism affecting ion channels, and it can be safely used in many cases (13). Because BrS arrhythmias occur mostly at night, at rest, or when the vagal tone is active, the increase in parasympathetic tone and use of parasympathomimetic drugs increase the risk of arrhythmias. Therefore, careful use of neostigmine, a parasympathomimetic agent, is recommended (9).

However, there are reports in the literature suggesting that there is no problem when used in combination with atropine (10). Additionally, because all local anesthetics block the sodium channel, they should be considered in terms of arrhythmia. Unlike lidocaine, local anesthetics such as bupivacaine and ropivacaine, which have a long-lasting effect, require particular attention. Their use in BrS is controversial, with case reports of ventricular arrhythmia following their use (14). Lidocaine, being short-acting, is likely safer and should be preferred over other local anesthetics. Beta-adrenergic blockade and alpha-

receptor agonists can exacerbate ST segment changes in BrS patients; this can be prevented with beta-agonists or alpha-blockade (15). In cases of increased vagal tone and bradycardia, it is recommended to administer atropine and ephedrine (1).

Conclusion

General anesthesia is the preferred method in the anesthesia management of patients with BrS. However, high-quality data are still inconclusive, and more comprehensive records are needed to understand the safety of commonly used drugs. Unlike our case, in patients who do not provide a detailed medical history, symptoms that may be associated with arrhythmia, such as sudden death at an early age in the family, cardiac diseases in family members, unexplained syncope, dizziness, shortness of breath especially at night, palpitations, and seizures, should be carefully investigated. Minimal ECG variability may be overlooked if not evaluated in this context. During the perioperative period, anesthesiologists should focus on autonomic changes, avoid superficial anesthesia and inadequate analgesia, minimize position changes, correct electrolyte imbalances, and maintain normothermy, normocarbia, and normovolemia. A defibrillator should be readily available in the operating room, just in case.

Ethics

Informed Consent: Informed consent was obtained from the patient.

Authorship Contributions

Surgical and Medical Practices: S.A., Y.C.A., Design: S.A., Y.C.A., Analysis or Interpretation: Y.C.A., Literature Search: S.A., Writing: S.A.

Conflict of Interest: No conflict of interest was declared by the authors.

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CASE REPORT

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De Novo Triple Negative Breast Cancer Development in a Patient Who had Lipofilling for Esthetic Reasons

Estetik Nedeniyle Lipofilling Yapılan Hastada *De Novo* Üçlü Negatif Meme Kanseri Gelişimi

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Abstract

Lipofilling has gained increased confidence in both esthetic and reconstructive breast surgery. However, in breast carcinoma patients there are some doubts about the crosstalk between adipose tissue microenviroment and cancer tissue. In our case report, a 48-year-old female patient with a heterozygous pathogenic variant in the chromosome *17 BRCA 1* gene had a history of lipofilling after loss of breast prosthesis. The patient presented with the development of triple negative breast carcinoma 20 months after lipofilling application. This case again raises the question about the risk of lipofilling on breast cancer development.

Keywords: Adipose tissue, breast cancer, lipofilling

Öz

Lipofilling uygulaması hem estetik hem de rekonstrüktif meme cerrahisinde güvenirlik kazanmıştır. Ancak meme kanseri hastalarında yağ dokusu mikro çevresi ile kanser dokusu arasında oluşabilecek etkileşim konusunda bazı şüpheler vardır. Olgu sunumumuzda kromozom *17 BRCA 1* geninde heterozigot patojenik varyant bulunan 48 yaşındaki kadın hastanın meme protezi kaybı sonrası lipofilling öyküsü mevcuttu. Hasta lipofilling uygulamasından 20 ay sonra üçlü negatif meme kanseri gelişimi ile başvurdu. Bu durum lipofilling işlemi sonrası meme kanseri risk artışına ilişkin soruları bir kez daha gündeme getirmektedir.

Anahtar kelimeler: Lipofilling, meme kanseri, yağ dokusu

Introduction

Lipofilling has gained popularity in breast surgery for esthetic and reconstructive purposes. It is efficent to correct volume defects with minimal scarring, improve esthetic results and lead to increase in patient satisfaction rate (1,2). On the other hand, the oncologic safety of lipofilling in the context of breast reconstruction is still a matter of controversy (3). Adipose tissue is a rich source of adipose tissue derived stem cells and growth factors. As a result of lipofilling, inflammation and remodeling processes occur at the recipient tissue. Up to now, it remains unclear whether this adipose tissue-breast cancer interactions really have the ability to stimulate breast cancer progression. A careful oncological follow-up is recommended for breast cancer patients after lipofilling (4,5).

In this article, we presented a case of a 48-year-old woman with triple negative breast cancer development in the left breast 20 months after lipofilling for esthetic reasons.

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Case Report

A 48-year-old female patient applied to our clinic with a complaint of a palpable mass in her left breast.

On the physical examination of the patient, a hard mass of approximately 3 cm in the upper inner quadrant and widespread nodular lesions in the left breast were detected. No lymphadenopathy was present in the bilateral axilla.

Particularly in the patient's medical history, she had bilateral augmentation mammoplasty surgery with breast implants in 1997. There was replacement of the left-side implant in 2012 due to implant complications. Removal of the left implant and lipofilling was done in January 2021. Breast ultrasound and magnetic resonance imaging scans performed at that time showed no suspicious findings for cancer in either breast.

The patient complained of palpable hardness in the left breast after six months after fat injection. The mammographic evaluation was consistent with fat necrosis in the middle inner quadrant of the left breast and superimposed on the pectoral muscle in the deep plane.

She noticed increase in the size of the mass in the left breast after one year. In the radiological evaluation performed in August 2022, there was a 27*16 mm sized, BIRADS 5 solid mass lesion in the upper inner quadrant of the left breast and lymphadenopathy, the largest of which was 19 mm in diameter and showed cortical thickening (5.5 mm) detected in the axilla (Figures 1, 2).

Tru-cut biopsy results from the patient's mass in the left breast were invasive breast carcinoma, grade 3, ER-, PR-, HER2-, Ki-67; 60-70%. The pathology results from the axillary lymph nodes were benign.

In genetic testing, a heterozygous pathogenic variant was detected in the chromosome *17 BRCA 1* gene (c.66dup-pGlu23Argfrester18). In her family history, her aunt had colectomy for colon carcinoma.

With those findings, the patient was evaluated at the oncology council and the patient underwent neoadjuvant chemotherapy. After chemotherapy, a radiological complete response was detected in the mass.

In May 2023, nipple skin sparing mastectomy, axillary sentinel lymph node sampling and breast reconstruction was performed for the left breast. The pathology results of the patient revealed no residual invasive carcinoma (complete response), and no metastasis in the axillary lymph nodes (0/4).

Discussion

Lipofilling has been used in the last century for filling defects and remodeling body shape. It is an extremely useful tecnique in esthetic and reconstructive breast surgery as well. The multipotent stem cells found in adipose tissue has regenerative potential. Patients are more satisfied with the appearance of their breast and showed an improved psychosocial, sexual, and physical well-being after breast surgery. They also have significantly lower implant complications, capsular contracture rate, and

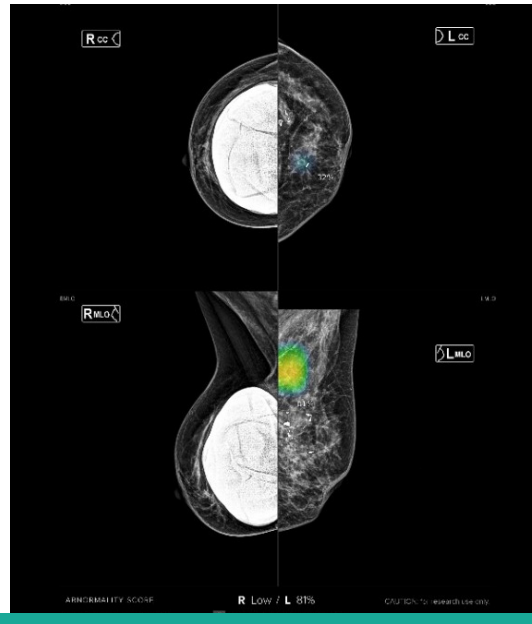

Figure 1. Malignant-looking mass in the left breast confirmed by artificial intelligence application in mammography

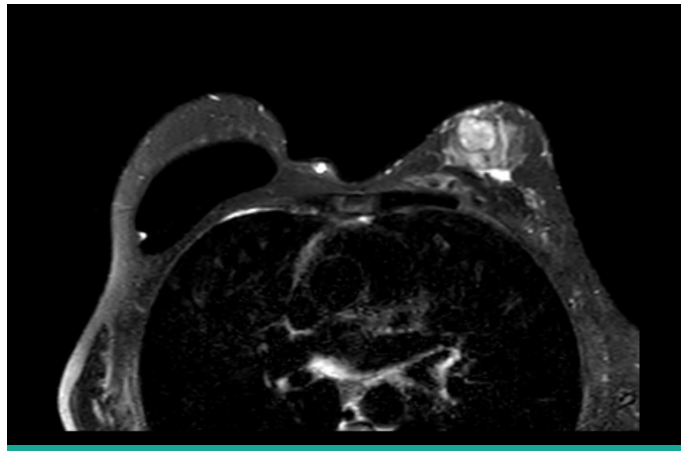

Figure 2. Breast MRI shows a well-circumscribed heterogeneous contrast-enhancing lesion in the upper inner quadrant of the left breast and prosthesis in right breast

MRI: Magnetic resonance imaging

breast pain as a result of the regenerative potential of the fat tissue (1,2,6). In the previous studies conducted on healthy BRCA mutation carriers, lipofilling was regarded as an oncologicaly safe method after prophylactic mastectomy (7,8).

However, fat tissue with its stem cells, adipokines and vascular-inducing factors may have pro-tumorigenic potential. Crosstalk between this mesenchymal stem cells and epithelial cells have the ability to participate in primary and metastatic tumor development and progression (9,10). A remarkable role of adipose tissues in cancer development as increased breast cancer proliferation and enhanced agresiveness was shown in animal and *in vitro* studies (2,11-13). On the other hand, there were no clearly demonstrated cancer recurrence risk increase in clinical studies (5,14). One of the rare clinical studies showing an increased local event risk was reported by Petit et al. (4). They showed increased intraepithelial neoplasia risk. They took attention to increased risk of local recurrence in women <50 years, with high grade neoplasia, Ki-67 ≥14 who had undergone quadrantectomy. They reported that cancer recurrence happened generally three to four years after lipofilling (4). Similarly, Berti et al. (15) conducted a retrospective study on breast carcinoma patients and compared survival and local recurrence rates between patients with lipofilling and without lipofilling. They showed that, lipofilling was an independent predictive factor for local recurrence in invasive breast carcinoma patients (15).

The risk of inducing *de novo* carcinogenesis after lipofilling is a very rare circumstance. Cheng et al. (16) presented a case with musinous carcinoma, discovered 2 months after lipofilling. As invasive breast carcinoma development from carcinoma *in situ* was 3-5 years according to the literature, they took attention to the short time interval after lipofilling to breast carcinoma development (16).

Conclusion

In our case report, we presented a patient being BRCA1 heterozygous positive and *de novo* development of triple negative breast carcinoma shortly after fat injection. Although previous studies have reported that lipofilling is generally safe even in patients with BRCA mutation, we would like to emphasize once again that caution should be exercised in these procedures.

Ethics

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

Authorship Contributions

Concept: N.T., Design: N.T., Data Collection or Processing: N.T., Analysis or Interpretation: N.T., O.C.Y., Drafting Manuscript: N.T., Critical Revision of Manuscript: N.T., O.C.Y., Final Approval and Accountability: N.T., O.C.Y., Technical or Material Support: N.T., O.C.Y., Supervision: N.T., O.C.Y., Writing: N.T., O.C.Y.

Conflict of Interest: No conflict of interest was declared by the authors.

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