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Research article

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Fabry disease prevalence in patients with familial Mediterranean fever: A cohort study

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Abstract

Background/Aim: Fabry disease is an X-chromosome inherited disease, which constitutes a rare disease group. Fabry disease has a wide spectrum of symptoms and some of these symptoms that are seen in other diseases. Familial Mediterranean fever (FMF) is a common disease in countries along the Mediterranean coast, including our country. Although typical episodes of recurrent high fever and abdominal pain occur, patients can also present with nonspecific symptoms and signs. This study aimed to investigate the presence of Fabry disease in patients with FMF.

Methods: Information about this cohort study was given to all patients who were followed up with a diagnosis of FMF. Those who agreed to sign the informed consent form were included in the study. Fabry disease screening was performed by galactosidase alfa (GLA) gene analysis in female patients and by examining lysosomal alpha galactosidase A (AGALA) enzyme activity in male patients. When enzyme activity was found to be low in male patients, a GLA gene analysis was also performed.

Results: Fabry disease was screened in a total of 189 patients with familial Mediterranean fever, and it was not detected in any of our patients. Low AGALA enzyme activity was detected in approximately 20% of the male patients. In the GLA gene analysis performed on these patients, any genetic mutation that could be associated with Fabry disease was not detected.

Conclusion: People with Fabry disease or FMF can present with common symptoms, such as arthritis, proteinuria, and abdominal pain. In our study, Fabry disease was not found in any of patients who had a diagnosis of FMF. However, only a few publications on this subject are available. In studies conducted in our country and around the world, it has been shown that GLA gene mutations that may cause Fabry disease can be detected in patients with FMF. However, such a mutation was not detected in our study.

Keywords: Alpha-galactosidase, Fabry disease, Familial Mediterranean fever

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Introduction

Fabry disease is an X-linked lysosomal storage disorder that is characterized by accumulation of globotriaosylceramide and globostriaosylsphingosine within lysosomes in almost all cells [1]. The GLA gene is mutated in Fabry disease that expresses alpha-galactosidase A (AGALA) enzyme activity and is located in the long arm of X chromosome (Xq22.1) [2]. The prevalence of Fabry disease differs among races and is reported to be seen from 1/8500 to 1/117,000 in Caucasian populations [3, 4]. It is known that prevalence of Fabry disease is probably underestimated because of nonspecific manifestations, wrong initial diagnosis, and lack of consideration of this disease by a clinician due to its rare occurrence. The Fabry Outcome Survey showed that rheumatological conditions, arthritis, neuropsychological diseases, Meniere disease, irritable colon, and/or chronic kidney disease of unknown etiology are the most commonly initial diagnoses in a patient with Fabry disease [5, 6]. Patients with Fabry disease may present with a wide spectrum of clinical manifestations. Acroparesthesias, angiokeratomas, abdominal pain, recurrent vomiting, corneal opacities, proteinuria, polyuria, unexplained renal insufficiency, and hypohidrosis are some clinical manifestations of Fabry disease.

Familial Mediterranean fever (FMF) is also a hereditary disorder [7]. A mutation in the pyrin (MEFV) gene causes FMF. FMF is almost always inherited in an autosomal recessive pattern. The MEFV gene is localized within the 16th chromosome and encodes pyrin. Recurrent fever, abdominal pain, chest pain, arthritis, and skin lesions may be seen in a patient with FMF [7–11]. The most important complication of FMF is amyloidosis, which can lead to chronic kidney disease and end stage renal disease [12]. Tel-Hashomer criteria are usually used to diagnose FMF [13]. Since most of the symptoms and signs of FMF are nonspecific, other accompanying diseases may sometimes be overlooked or make some diseases difficult to diagnose [14].

Fabry disease and FMF have some similar manifestations and only a few studies investigating Fabry disease prevalence in patients with FMF are available. In this study, we aimed to investigate Fabry disease prevalence in patients with FMF.

Materials and methods

Patients

All patients who were followed up by our outpatient clinic with the diagnosis of FMF between May 2018 and June 2020 and agreed to participate in this cohort study were included. Diagnosis of all patients was obtained with Tel-Hashomer criteria. Demographic data and clinical features of patients were obtained with face-to-face interviews. MEFV gene mutations were recorded from patients' files. Informed consent was taken from all patients for Fabry disease screening. Local Ethics Committee approval was taken from the Afyonkarahisar Health Sciences University Clinical Research Ethics Committee (date: 21/08/20, decision number: 362).

Fabry Disease Screening

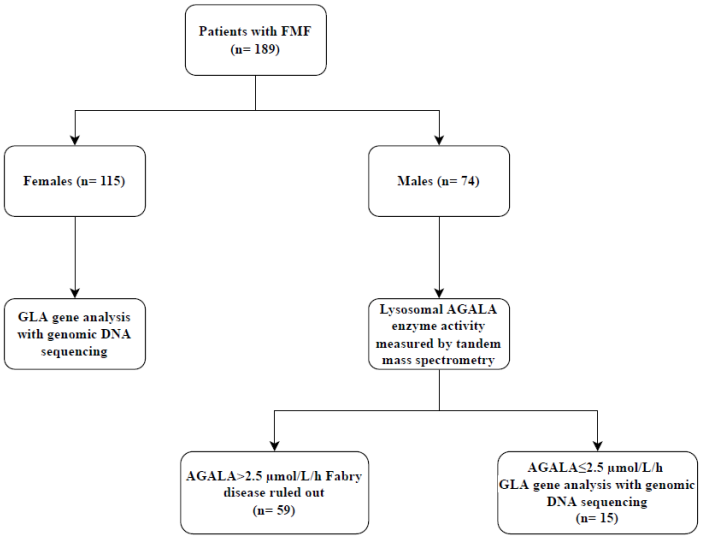
AGALA enzyme activity

Lysosomal AGALA enzyme activity was evaluated in male patients. Samples for enzyme activity were included on dried blood spots (DBS). Tandem mass spectrometry was used as method. AGALA > 1.2 µmol/l/h was considered the cut-off value. GLA gene analysis also was done for male patients having AGALA < 2.5 µmol/l/h.

GLA gene mutation

Peripheral blood samples were collected in ethylenediaminetetraacetic acid (EDTA) tubes for GLA gene analysis. Analysis was performed using a genomic DNA sequencing method in female patients. Exons 1–7 were examined for all females. Figure 1 shows the method by which patients are screened for Fabry disease.

Figure 1: Fabry disease screening in study patients



Statistical analysis

SPSS 22.0 (SPSS IBM, Armonk, NY, USA) is used for statistical analysis. Categorical variables were expressed as number and percentage. The Shapiro–Wilk test was used to determine normal distribution of continuous variables. Numeric variables were presented as mean (standard deviation) or median (min–max) according to their normality.

Results

The study was conducted with 189 patients with FMF. Of these, 60.8% (n = 115) were female, and 39.8% (n = 74) were male. The median age of patients was 38 years (range: 18–74 years). Patient evaluations in terms of Tel-Hashomer criteria are shown in Table 1.

The results of the MEFV gene analysis are shown in Table 2.

Table 1: FMF characteristics of the patients

Criteria	Present (%-n)
Recurrent febrile episodes associated with serositis	70.4–133
Amyloidosis of AA type	9.5–18
Response to colchicine	94.7–179
Recurrent febrile episodes	74.6–141
Erysipelas-like erythema	18–34
Positive family history	73.5–139

Table 2: Mutations in the pyrin (MEFV) gene

Mutation	%-n
m694v (homozygous)	16.4–31
Wild type	16.4–31
m694v (heterozygous)	15.9–30
m694v (heterozygous), m680i (heterozygous)	10.1–19
m694v (heterozygous), v726a (heterozygous)	7.9–15
e148q (heterozygous)	3.7–7
m680i (heterozygous)	3.7–7
m694v (heterozygous), r761h (heterozygous)	3.2–6
m694v (heterozygous), a744s (heterozygous)	2.6–5
m694v (heterozygous), e148q (heterozygous)	2.6–5
v726a (homozygous)	2.6–5
m680i (homozygous)	2.6–5
m694i (heterozygous), v726a (heterozygous)	2.1–4
m694v (heterozygous), v726a (heterozygous)	2.1–4
v726a (heterozygous)	2.1–4
m680i (heterozygous), v726a (heterozygous)	1.6–3
p369s (heterozygous)	1.1–2
m680i (homozygous) or m694i (heterozygous) or other heterozygous compound	3–6
Total	100–189

Median FMF duration was 6 years (range: 1–40 years). Hypertension was present in 9.5% (n = 18) of the patients, diabetes mellitus in 6.3% (n = 12), chronic kidney disease in 7.9% (n = 15), and coronary artery disease in 0.5% (n = 1). None of the patients had a history of cerebrovascular events.

GLA gene analysis of all female patients was negative. The mean alpha-galactosidase A level of male patients was 4.28 (1.6) μmol/l/h. In 20.3% (n = 15) of male patients, the AGALA enzyme level was ≤ 2.5 μmol/l/h, and GLA gene analysis was also performed for these patients. No mutations were detected in the GLA gene of these male patients.

Discussion

Fabry disease is classified in the rare disease group, and its prevalence differs in studies. The prevalence of Fabry disease is underestimated due to the rarity of the disease, its non-specific symptoms, and the misdiagnosis of patients [4]. In the Fabry Outcome Survey, it was shown that misdiagnosis of Fabry disease is common. Male patients are diagnosed 13.7 years after the first symptom, and female patients are diagnosed 16.3 years after the first symptom [6]. Most patients with FMF experience their first attacks in childhood. The first attack occurs before the ages of 10 and 20 years in 65% and 90% of cases, respectively [7]. Patients with FMF may experience a prodromal period 1–2 days before an attack. Constitutional symptoms, neuropsychiatric or physical signs, appetite and taste alterations, and pain in the region in which the flare-up will appear may be seen in the prodromal period [15]. Our study was designed based on the view that both Fabry disease and FMF have common nonspecific symptoms; however, no patients with Fabry disease in our FMF patients were found.

FMF is a clinical diagnosis, and genetic analysis is not a test used for the diagnosis of FMF. Genetic testing of the MEFV gene show be wild type in some patients with FMF. A wild type MEFV gene does not mean that these patients do not have FMF, but more detailed research may be required to interpret this finding in these patients. The prevalence of Fabry disease varies between studies according to the selected patient group [16–19]. In a study conducted by Zizzo et al. [20], it was shown that 9.4% (n = 3) of FMF patients having a MEFV gene with a single genetic alteration or without any mutation had some exonic mutations in GLA genes responsible for Fabry disease. They concluded that patients with ambiguous symptomatic FMF patterns should be screened for Fabry disease. Lidove et al also showed that two out of 58 patients with Fabry disease had previously been diagnosed with FMF [21]. Huzmeli et al. [22] found a mutation in GLA gene in one out of 177 patients with FMF. The genetic mutation detected in Huzmeli's study was D313Y, which is considered a benign mutation. The D313Y is the most discussed mutation in the literature [23–25]. In fact, some studies have reported false higher prevalence due to D313Y [25, 26]. Fabry disease was not detected in any of the 189 FMF patients in our study. In the TURKFAB study, Turkmen et al. [28] found the incidence of Fabry disease in patients with chronic kidney disease of unknown etiology to be 0.95% (3/313). The study was carried out with focus on chronic kidney patients who did not receive renal replacement therapy, and enzyme replacement therapy was also started in patients with Fabry disease, which could lead to end-stage renal disease. Both FMF and Fabry disease may lead to serious renal complications. Our study was designed based on the premise that Fabry disease and FMF may have similar clinical features. However, Fabry disease was not found in our patients with FMF in this study.

Limitations

The limitations of our study are the single center and the small population of 189 patients with respect to a disease that is common in our country such as FMF is. However, the limited number of publications in the literature investigating the frequency of Fabry disease in patients with FMF makes our study important. More comprehensive studies are needed to investigate the frequency of Fabry in FMF patients.

Conclusion

Fabry disease is an awareness disorder. According to our literature review, our study is the largest study investigating the frequency of Fabry disease in FMF patients. Although mutations that may be associated with Fabry disease were found in the literature in patients with FMF, no FMF patients with Fabry disease were found in our study.

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Research article

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A retrospective cohort study of the change in inflammatory parameters in childhood schizophrenia and bipolar disorder from childhood to adulthood

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Ethics Committee Approval
Ethics committee approval was received for the study from the Dicle University Faculty of Medicine ethics committee (Number: 393 and Date: 16/07/2020).
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Abstract

Background/Aim: The etiologies of childhood schizophrenia and bipolar disorder have not yet been clarified. In cases in which the symptoms of mood are not dominant and psychotic symptoms are more dominant, it may be difficult to distinguish between childhood schizophrenia and bipolar disorder diagnoses. Follow-up studies concerning this subject have indicated that approximately half of the adolescents diagnosed with bipolar disorder were first (and incorrectly) diagnosed with schizophrenia. Therefore, strong markers are still needed to be used in the differential diagnosis at the time of the first application. An increase in the number of studies on the neuroinflammatory process in pediatric schizophrenia and bipolar illness have started to appear in the literature. The neutrophil–lymphocyte, thrombocyte–lymphocyte, and thrombocyte–neutrophil ratio (NLR, TLR, and TNR, respectively) levels in patients with childhood schizophrenia and childhood bipolar disorder at the time of admission and five years later were evaluated to determine whether inflammatory markers changed over time.

Methods: Twelve patients diagnosed with childhood schizophrenia and 14 patients diagnosed with childhood bipolar disorder were included in the study. Active infections, medical, neurological, endocrine, and metabolic illnesses, mental retardation, further concomitant psychiatric diagnoses, and intoxication were all exclusion factors. Hemograms from the same patients who satisfied the inclusion criteria when they originally applied and again at the fifth year follow-up were evaluated. Age, gender, neutrophil, lymphocyte, leukocyte, and thrombocyte values were recorded. NLR was calculated by dividing the neutrophil count by lymphocyte count. TLR value was calculated by dividing the thrombocyte count by lymphocyte count. TNR value was calculated by dividing the thrombocyte count by neutrophil count. Bipolar disorder and schizophrenia status were compared using NLR, TLR, and TNR parameters both at the time of initial diagnosis and at the fifth year of follow-up.

Results: When the initial admission hemograms of patients with childhood schizophrenia or childhood bipolar disorder were examined, no statistically significant differences between the two groups in terms of NLR (P = 0.150) and TLR (P = 0.440) were found. TNR was significantly higher in childhood bipolar disorder patients than in childhood schizophrenia (P = 0.015). At the fifth year follow-up, the hemograms of individuals diagnosed with either childhood schizophrenia or childhood bipolar disorder were compared, and no statistically significant differences between the two groups in NLR, (P = 0.572),TLR (P = 0.758), and TNR (P = 0.328) were found.

Conclusion: It was concluded that NLR and TLR levels did not change significantly over time in either disease and could not be used for the differential diagnosis of either disease. TNR may be considered for differential diagnoses in childhood schizophrenia and bipolar disease, particularly at the time of the first episode after confirmation of this study's findings with future studies.

Keywords: Childhood, Schizophrenia, Bipolar, NLR, TLR, TNR

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Introduction

Although the etiologies of schizophrenia and bipolar disorder are unknown, these conditions are caused by changes and different interactions in or outside the central nervous system due to a variety of factors. These conditions are mental disorders that cause a significant deterioration in functionality and quality of life [1, 2]. While very early-onset schizophrenia seen before the age of 13 is seen in 1 in 40,000 children, the incidence of early-onset schizophrenia before the age of 18 is 50 times higher than very early-onset schizophrenia. The lifetime prevalence of schizophrenia is 1% worldwide [3]. Bipolar disorder, on the other hand, has been found to affect between 0.1% and 2.5% of children and adolescents in studies in the literature [4, 5]. At the same time, bipolar disorder in children and adolescents is a serious illness that causes severe functional decline and can result in repercussions, such as recurrent hospitalizations and suicide attempts [6].

Microglia are thought to be brain macrophages, and these cells can contribute to neurodegeneration by altering the oxidant–antioxidant balance and activating the production of numerous proinflammatory cytokines in response to even minor pathogenic changes in the brain [7]. According to some research, the increase in cytokines linked with this neuroinflammatory process that begins in the central nervous system may influence the blood–brain barrier and have repercussions on the current condition in the peripheral inflammatory system [8]. Neutrophil/lymphocyte and thrombocyte/lymphocyte ratios (NLR and TLR, respectively), which are simple and inexpensive indicators of systemic inflammation, are used as biomarkers in cancer and some systemic diseases [9, 11]. Furthermore, various studies have been conducted to demonstrate the usability of these ratios as biomarkers in both psychotic and mood disorders to shed light on early diagnosis and etiology [12, 13].

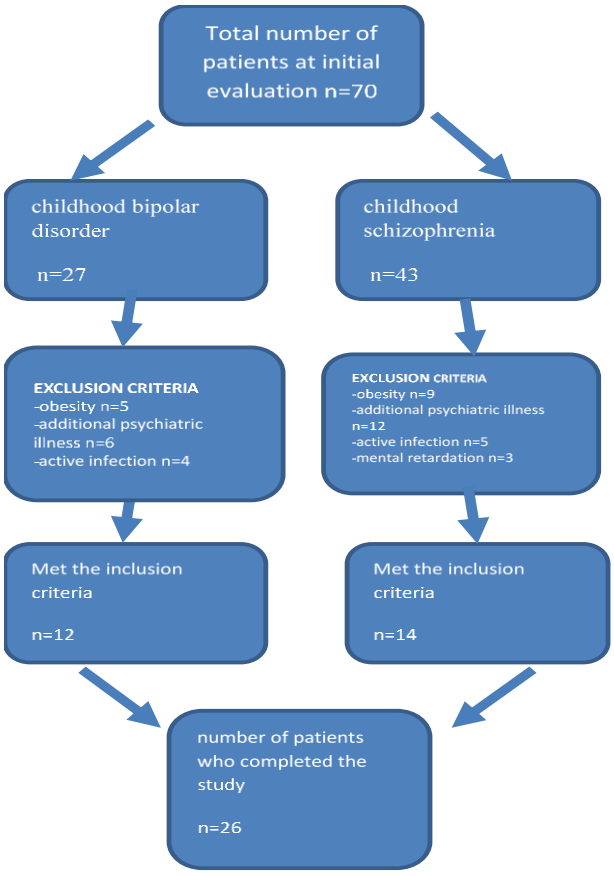
In cases in which the symptoms of mood are not dominant and psychotic symptoms are more dominant, it may be difficult to distinguish between a diagnosis of childhood schizophrenia and one of bipolar disorder. The follow -up studies on this subject show that approximately half of the adolescents diagnosed with bipolar disorder were first diagnosed (incorrectly) with schizophrenia [14, 15]. Therefore, strong markers are still needed to be used in the differential diagnosis at the time of the first application.

However, only a few investigations on how the neuroinflammatory process affects individuals with childhood schizophrenia and bipolar disorder over time have been published. NLR, TLR, and thrombocyte/neutrophil (TNR) levels of patients who were diagnosed with either or both schizophrenia and bipolar disorder as children and who are still being followed up and treated were evaluated. The study aimed to examine how the neuroinflammatory process changes throughout the disease in childhood schizophrenia and bipolar disorder. In addition, the use of NLR, TLR and TNR levels for differential diagnosis of these two diseases were examined.

Materials and methods

Our study was performed by scanning the records of our child and adolescent mental health and illness clinic and adult mental health and diseases clinic between September 1, 2013, and September 1, 2020. The required ethics committee approval (Date:16/07/2020-No:393) was obtained from the Ethics Committee for Non-Interventional Clinical Research, Dicle University Faculty of Medicine, for this study. Patients who presented to our child and adolescent psychiatry outpatient clinic with their first psychotic attack, had not yet been treated, and were diagnosed with schizophrenia in DSM-5 follow-ups, and patients who presented with their first manic attack had not yet begun medical treatment and were diagnosed with bipolar disorder 1 based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) follow-ups were considered for this study. The study was planned with the inclusion of the patients who fulfilled study requirements. Patients diagnosed with schizophrenia without positive symptoms after clinical evaluation using the Positive and Negative Syndrome Scale at their fifth year follow-ups and patients with bipolar disorder in the euthymic phase (Young Mania Rating Scale score ≤ 5 and Hamilton Depression Rating Scale score ≤ 7) were re-evaluated [16-18]. Active infections, medical, neurological, endocrine, and metabolic illnesses, mental retardation, further concomitant psychiatric diagnoses, and intoxication were considered exclusion factors. The study consisted of 12 patients with childhood schizophrenia who satisfied all criteria and 14 individuals with childhood bipolar disorder out of the 70 patients who fulfilled just the diagnostic and follow-up requirements (Figure 1).

Figure 1: Study group follow-up diagram



Hemograms at first admission and five years later were examined for patients who met the inclusion criteria. Complete blood count was calculated by Cell-Dyn 3700 (Abbott Diagnostics, USA). Age, gender, neutrophil, lymphocyte, leukocyte, and thrombocyte values were recorded. NLR was calculated by dividing the neutrophil by lymphocyte value. TLR value was calculated by dividing the thrombocyte by lymphocyte

value. TNR was calculated by dividing the thrombocyte by the neutrophil value.

Statistical analysis

IBM SPSS 21.0 for Windows Statistical Package Program was used for the statistical evaluation of our research data. The mean and standard deviation (SD) of measured variables were reported, whereas categorical variables were presented as numbers and percentages (%). It was determined whether the data conformed to the normal distribution. Does not show normal distribution; Wilcoxon Test was used to compare the previous and next groupings. The Mann Whitney-U test was used to compare two independent groups. A statistically significant result was accepted if *P*-value ≤ 0.05.

Results

In the first phase, the study was started with 70 patients. The study was terminated with 26 patients who met the inclusion criteria (Figure 1). The mean age of 12 patients (five boys, seven girls) diagnosed with childhood schizophrenia was 19. The mean age of 14 patients (eight boys, six girls) diagnosed with childhood bipolar disorder was 19. No significant differences between groups with respect to age and gender were found (P = 0.725, P = 0.630).

When the hemograms of patients who presented with the first childhood psychotic episode and were diagnosed with schizophrenia during follow-ups were compared to the hemogram of the same patients who did not have positive symptoms during the fifth year follow-up, no statistically significant differences in terms of NLR, TLR, and TNR levels during the follow-up period were found (P = 0.730, P = 0.925, P = 0.470, respectively) as shown in Table 1.

Table 1: Comparison of hematological parameters between patients who presented with the first childhood psychotic episode and were diagnosed with schizophrenia during the fifth year follow-up from childhood to adulthood

Hematological Parameter	Period	Median	Mean (SD)	Z	*P*-value
WBC	Childhood	9.09	9.54 (3.38)	0.157	0.875
	Adulthood	8.90	9.46 (1.96)		
TRM	Childhood	238.60	251.07 (79.87)	2.354	0.061
	Adulthood	250.80	285.45 (119.93)		
LYM	Childhood	2.11	2.22 (0.72)	0.565	0.572
	Adulthood	2.38	2.42 (0.75)		
NEU	Childhood	6.04	6.46 (3,12)	0.157	0,875
	Adulthood	5.53	6.17 (1.95)		
NLR	Childhood	2.64	3.41 (3.00)	0.345	0.730
	Adulthood	2.70	2.86 (1.38)		
TLR	Childhood	103.89	124.86 (58.52)	0.094	0.925
	Adulthood	121.00	128.51 (66.56)		
TNR	Childhood	37.34	46.32 (29.70)	0.722	0.470
	Adulthood	43.09	48.89 (22.92)		

n: 14, Median: median value, Mean Rank: Ranks Average, SD: standard deviation, Z: Wilcoxon Signed Rank test value, *P*: Wilcoxon Signed Rank test statistical significance value WBC: white blood cell, TRM: thrombocyte, LYM: lymphocyte, NEU: neutrophil, NLR: neutrophil/lymphocyte ratio, TLR: thrombocyte/lymphocyte ratio, TNR: thrombocyte/neutrophil ratio

When the hemograms of patients who had their first manic episode as children and were diagnosed with bipolar disorder during the follow-up period were compared to the hemograms of the same patients who were in the euthymic phase at the fifth year follow-up, no statistically significant differences in terms of NLR, TLR, and TNR levels were found (P = 0.480, P = 0.583, and P = 0.136) as shown in Table 2.

When the first admission hemograms of patients with childhood schizophrenia and childhood bipolar disorder were examined, no statistically significant differences between the two groups in terms of NLR (P = 0.150) and TLR (P = 0.440) were found, but a statistically significant difference in TNR was noted (P = 0.015) as shown in Table 3.

Table 2: Comparison of hematological parameters between patients who had their first manic episode as children and were diagnosed with bipolar disorder during the fifth year follow-up

Hematological Parameter	Period	Median	Mean (SD)	Z	*P*-value
WBC	Childhood	7.70	8.10 (1.79)	1.647	0.099
	Adulthood	8.22	8.72 (2.49)		
TRM	Childhood	295.25	291.90 (74.39)	0.628	0.530
	Adulthood	272.65	275.98 (45.34)		
LYM	Childhood	2.31	2.36 (0.66)	0.078	0.937
	Adulthood	2.25	2.31 (0.68)		
NEU	Childhood	4.49	4.87 (1.85)	1.648	0.099
	Adulthood	4.89	5.56 (2.25)		
NLR	Childhood	1.94	2.33 (1.39)	0.706	0.480
	Adulthood	2.50	2.58 (1.23)		
TLR	Childhood	116.05	129.46 (38.52)	0.549	0.583
	Adulthood	118.49	126.06 (31.30)		
TNR	Childhood	67.90	68.69 (31.11)	1.490	0.136
	Adulthood	47.96	56.90 (22.72)		

n: 12, Median: median value, Mean Rank: Ranks Average, SD: standard deviation, Z: Wilcoxon Signed Rank test value, P: Wilcoxon Signed Rank test statistical significance value, WBC: white blood cell, TRM: thrombocyte, LYM: lymphocyte, NEU: neutrophil, NLR: neutrophil/lymphocyte ratio, TLR: thrombocyte/lymphocyte ratio, TNR: thrombocyte/neutrophil ratio

Table 3: Comparison of hematological parameters between patients diagnosed with childhood psychosis and those diagnosed with childhood bipolar disorder

Hematological Parameter	Diagnosis	n	Median	Mean (SD)	U	*P*-value
WBC	Bipolar	12	7.70	8.10 (1.79)	63.00	0.280
	Psychosis	14	9.09	9.54 (3.38)		
TRM	Bipolar	12	295.25	291.90 (74.39)	54.00	0.123
	Psychosis	14	238.60	251.07 (79.87)		
LYM	Bipolar	12	2.31	2.40 (0.66)	72.50	0.554
	Psychosis	14	2.11	2.22 (0.72)		
NEU	Bipolar	12	4.49	4.87 (1.85)	56.00	0.150
	Psychosis	14	6.04	6.46 (3.12)		
NLR	Bipolar	12	1.94	2.33 (1.39)	56.00	0.150
	Psychosis	14	2.64	3.41 (3.00)		
TLR	Bipolar	12	116.05	129.46 (38.52)	69.00	0.440
	Psychosis	14	103.89	124.86 (58.52)		
TNR	Bipolar	12	67.90	68.69 (31.11)	37.00	0.015
	Psychosis	14	37.34	56.64 (31.84)		

n: number, Median: median value, Mean Rank: Ranks Average, SD: standard deviation, U: Mann Whitney U test value, P: Mann Whitney U test statistical significance value, WBC: white blood cell, TRM: thrombocyte, LYM: lymphocyte, NEU: neutrophil, NLR: neutrophil/lymphocyte ratio, TLR: thrombocyte/lymphocyte ratio, TNR: thrombocyte/neutrophil ratio

At the fifth year follow-up, the hemogram of patients with childhood schizophrenia and childhood bipolar disorder were compared, and no statistically significant differences between the two groups were found in terms of NLR, (P = 0.572), TLR (P = 0.758), and TNR (P = 0.328) as shown in Table 4.

Table 4: Comparison of hematological parameters at the fifth year follow-up of the group diagnosed with childhood psychosis and the group diagnosed with childhood bipolar disorder

Hematological Parameter	Diagnosis	n	Median	Mean (SD)	U	*P*-value
WBC	Bipolar	12	8.22	8.72 (2.49)	65.50	0.341
	Psychosis	14	8.90	9.46 (1.96)		
TRM	Bipolar	12	272.65	275.98 (45.34)	73.00	0.572
	Psychosis	14	250.80	285.45 (119.93)		
LYM	Bipolar	12	2.25	2.31 (0.68)	77.50	0.738
	Psychosis	14	2.38	2.42 (0.75)		
NEU	Bipolar	12	4.89	5.56 (2.25)	68.00	0.411
	Psychosis	14	5.53	6.17 (1.95)		
NLR	Bipolar	12	2.50	2.58 (1.23)	73.00	0.572
	Psychosis	14	2.70	2.86 (1.38)		
TLR	Bipolar	12	118.49	126.06 (31.30	78.00	0.758
	Psychosis	14	121.99	128.51 (66.56)		
TNR	Bipolar	12	47.96	56.90 (22.72)	65.00	0.328
	Psychosis	14	43.09	48.89 (22.92)		

n: number, Median: median value, Mean Rank: Average of Ranks, SD: standard deviation, U: Mann Whitney U test value, P: Mann Whitney U test statistical significance value, WBC: white blood cell, TRM: thrombocyte, LYM: lymphocyte, NEU: neutrophil, NLR: neutrophil/lymphocyte ratio, TLR: thrombocyte/lymphocyte ratio, TNR: thrombocyte/neutrophil ratio

Discussion

Although schizophrenia is an uncommon diagnosis in both children and adolescents, it has substantial consequences for such young patients. Early diagnosis and an effective treatment regimen are expected to minimize losses in quality of life [19]. Again, in pediatric bipolar disorder studies, it has been reported that 70%–100% of patients recovered but recurred to 80% within 2 to 5 years, did not fully recover functionality, attempted suicide, engaged in substance abuse, and/or started having trouble with the

law; thus, early diagnosis is important for minimizing these issues [20–24].

No changes in these parameters were observed in long-term follow-ups in our study, which looked at the long-term consequences of the inflammatory process in individuals diagnosed with schizophrenia and bipolar disorder as children and whose diagnosis and treatment persisted into adulthood. Falcone et al. found a statistically significant increase in monocytes and lymphocytes in the first attack psychosis group compared to the control group in their research comparing blood parameters of 80 pediatric patients with an initial diagnosis of psychosis in 66 healthy children [25]. Ozdin et al. [26] discovered that NLR and TLR were substantially greater in the relapse phase compared to the control group in their research of 105 persons with schizophrenia and 105 healthy controls and that NLR and TLR declined significantly in the remission phase compared to the relapse period. Garcia-Rizo et al. [27] found no differences between the groups in 75 adult patients with the newly diagnosed psychotic conditions and 80 healthy controls in terms of NLR levels. It has been reported that since early-onset psychosis occurs during neurobiological development, it has more permanent effects on an individual in terms of cognitive and psychosocial deterioration, and the prognosis is worse than seen with adult-onset psychosis [28, 29]. In our investigation, the absence of differences in inflammatory markers in long-term follow-ups showed that this process may be connected to the progressive trajectory of this disease.

In our study, no differences were found between NLR, TLR, and TNR measured in the childhood bipolar phase and the euthymic phase at follow-up. In their study of bipolar patients, euthymic patients, and healthy controls, Kalelioğlu et al. [30] discovered that NLR and TLR increased in both bipolar and euthymic phases compared to healthy controls, but no differences in NLR and TLR between bipolar and euthymic phase in the same patients were found. Mazza et al. [12] regarded this scenario as distinct phases of bipolar illness that activated inflammatory processes differently, while a reduced inflammatory response, even though it is euthymic, may continue.

Childhood schizophrenia has a diverse clinical appearance, and other mental diseases, such as bipolar disorder and organic reasons, should be considered before making a diagnosis of schizophrenia [19]. Thrombocytes are hypothesized to be effective in endothelial permeability, neutrophil, and macrophage migration, and neuroinflammatory processes by activating the release of specific cytokines and neurotransmitters. It is predicted that monitoring these parameters may be effective in diagnosing/treating some psychiatric disorders [31]. Özdin et al. [32] compared NLR and TLR levels in patients with adult schizophrenia and bipolar disorder to those in the healthy control group and discovered that NLR, TLR, and thrombocyte counts were greater in the bipolar disorder group, whereas lymphocyte counts were lower. In schizophrenic patients, they found an increase in NLR and TLR values and a decrease in both neutrophil and lymphocyte counts compared to controls. It has also been reported that patients with schizophrenia have higher NLR values than those with bipolar disorder. Our study found that TNR was considerably greater in the bipolar disorder group when compared with children with schizophrenia and bipolar disorder who did use drugs, but this difference did not exist in adulthood. The fact that this difference was observed in the active disease phase and then disappeared in the remission phase for both disease groups led us to believe that TNR could be used in the differential diagnosis of mood disorder and schizophrenia during the first psychotic episode in childhood, which could cause diagnostic confusion. However, it was concluded that studies with a larger number of patients are needed to establish reference values for TNR.

Limitations

The limitations of our study include the limited number of patients and absence of a healthy control group in addition to patients receiving medical treatment during follow-up. Since these diseases are less common in childhood, the number of patients was limited. In addition, the five-year period, which can be considered long for a follow-up period, may have caused the number of patients to be even less. Since this study was carried out with a limited number of patients, the results should be supported by future studies.

Conclusion

Numerous unanswered problems regarding neuroinflammatory processes in pediatric schizophrenia and bipolar illnesses that cause severe functional loss and greatly affect the quality of life exist. It was concluded that NLR and TLR levels did not change significantly over time for both diseases and could not be used for the differential diagnosis of both diseases. TNR may be considered for differential diagnoses in childhood schizophrenia and bipolar disease, particularly at the time of the first episode; however, further confirmation of this study's findings is needed.

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Research article

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The effect of virtual reality glasses against the fear of circumcision: A randomized controlled trial

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Ethics Committee Approval
In order to conduct the research study, ethics committee permission was obtained from "Karaman University, Faculty of Health Scieces, Ethics Committee of non-Pharmaceuticals and non-Medical Device Researches" (dated 16/06/2017 and numbered 2017/975), and institutional permission was obtained from the "Ministry of Health Karaman Public Hospitals Institution General Secretariat of the Public Hospitals Association of Karaman Province" (dated 13/07/2017, and numbered 50658796-774.99-E.3674). Additionally, written consents were obtained from all of the participant patients and their parents conerning their volition to participate in the study. All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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

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Abstract

Background/Aim: Circumcision is an invasive operation that male children undergo in our country and some others. During this process, the child can experience fear, anxiety, and pain simultaneously. As a randomized controlled VR study, this research was conducted to determine the effect of virtual reality (VR) glasses on reducing fear/anxiety and pain during circumcision in children.
Methods: The study was conducted on 125 children (6-11 years old). The same healthcare team performed the circumcision of the children in both groups. The children were randomly split into VR and control groups. The children in the VR group, just before the circumcision, watched their preferred cartoon film via VR glasses. No additional procedure was applied to the children in the control group except for ordinary procedures in the hospital. The fear and pain status measured by Wong-Baker Faces Pain Rating Scale and Children Fair Scale of all the children were evaluated before and after the operation by the child, parents, and the observer. Descriptive statistics, chi-square, and t-tests analyzed the data.
Results: There was no significant difference between the groups regarding demographic characteristics such as age, BMI, previous hospitalization, and anesthetic drug used before the procedure of the children included in the study. Preoperative (VR = 1.03 (0.18), control = 1.05 (0.22)) and pre-procedural (VR = 2.61 (1.02), control = 2.33 (1.22)) fear levels were also similar ($P > 0.05$). After the procedure, it was determined that the mean duration of the procedure (365.36 (64.73) sec), crying time (21.31 (41.74) sec), and fear scores (0.36 (0.68)) of the children in the VR group were lower ($P < 0.001$). However, pain mean scores were similar ($P > 0.05$).
Conclusion: It is thought that watching a cartoon with VR glasses during the circumcision operation may be effective in reducing the child's fear level, crying, and operation time.

Keywords: Circumcision, Child, Fear, Pain, Virtual reality glasses

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Introduction

Circumcision is defined as the process of surgical removal of the foreskin, which covers the glans penis by cutting it in a certain way and length [1-5]. There are different applications concerning who makes the operation and where it is made. However, since this procedure is a surgical intervention, the most appropriate method is to conduct it under hospital conditions, even in surgery rooms [6-8].

Circumcision can be conducted at any age. However, since the child is exploring his sexual identity between 3-6 years, the children at these ages can experience a higher level of fear, worrying about losing their sexual organs. This situation, called castration anxiety, can cause psychological problems in the children [4, 9] and recovery from such problems can be difficult [2, 4, 10]. Therefore, it is reported that the most appropriate circumcision age is either before three years old or after six years old [2].

Just after the moment that the boy is informed about his circumcision, he starts to fear. As he doesn't know what to do, he can demonstrate various reactions such as a sense of shame due to revealing his external genital organ, the anxiety of pain, sleeplessness, uneasiness, resistance to those around him, and attacking. In addition, if the child witnesses a previous circumcision operation, it can influence the fear. In the studies conducted on adults, when the adults were asked what they felt about their circumcision operations, they generally stated a feeling of fear and anxiety [11, 12]. Therefore, it is important to use an effective fear-reducing method in fearful and anxious interventions in children [13, 14].

There are numerous approaches involving pharmacological and non-pharmacological methods for reducing the fear and anxiety that emerge during the children's medical operations. One of the most frequently applied non-pharmacological methods to eliminate fear and anxiety during medical operations is distraction. The distraction method is an attempt to focus the attention of the patient on another stimulus in order to decrease the pain; it is based on the hypothesis that the capacity of the mind is limited in focusing the attention on the stimulus [14]. During these processes, it is known that some methods are used, such as blowing up a balloon, distraction cards, listening to music, and kaleidoscope in order to distract the children [15-22]. In parallel with the recent technological developments, the use of virtual reality (VR) glasses was started in order for distraction in the health field. VR is a new technological development that children accept as a distraction and attraction way. This method is an intermediary in the individual-computer interaction, which helps the individual become an active participant in the virtual world through a combination of visual, auditory, and tactual stimuli [23]. Hoffman et al. [24] reported that VR is a "uniquely attractive setting " that successfully pulls away the children from most of their mental focuses and painful processes.

In the literature, it is emphasized that using VR glasses is an effective method in reducing the preoperative anxiety, decreasing the pain in the surgical operations with local anesthesia, medical dressing for burns in children, lumbar puncture in children with cancer, and during phlebotomy in the children [10, 13, 25-27]. However, in the institution where the research was conducted, there was no method to reduce the fear and the anxiety during circumcision operations, which is one of the most effective causes of fear/anxiety and pain in children. Therefore, by applying a method that has not been used during circumcision operations in children, this research study aims at revealing an effective, simple, economical, and practical method and shortening the operation time, which reduces the fear/anxiety and the pain. If positive results are obtained from this research study, and if it is proved to be an effective and reliable method in reducing the fear/anxiety and the pain, a contribution will be made to using a cheap and effective non-pharmacological method. Moreover, it is aimed at ensuring the children are able to simply tolerate procedures that create fear/anxiety and making contributions at national and international levels to a nursing care approach, which will minimize the fear/anxiety and pain for children in obligatory cases such as going to a hospital and being treated.

Materials and methods

Research type

This study was conducted as a Randomized Controlled Experimental Research design with a Pre-Test-Post-Test Control Group in order to determine the effect of virtual reality glasses applied during the procedure to reduce fear/anxiety and pain in children who will be circumcised between 6-11 years old.

Participants

The population comprised 6-11-year-old children who applied for circumcision at the Pediatric Surgery Unit of Karaman Public Hospital between January and August 2018. The sample size was calculated via the G*Power program, considering the known scores (4.53+3.23), with 95% strength, a 0.05 significance level, and 10% variation. Therefore, the sample size was determined as 116, but considering the risk of case loss, 64 children in VR and 61 children as control groups were grouped.

Inclusion criteria for the research;

The child should be between 6-11 years old (Min: 68 months),
The same surgeon should conduct the circumcision operation,
The child should have been given the standard information before the operation,
The surgery equipment used in operation should be the same,
The child should have the perception level to evaluate his fear/anxiety scale,
The child should not have a physical or mental illness,
The child should be able to communicate,
The child should not have any hearing, speaking, or sight problems,
The child should not have a chronic illness,
The child should not be using a continuous medicine,
The child should not have consumed analgesics in the last six hours,
The child should not have a health problem that triggers pain,
The child and his parents should accept participating in the research.

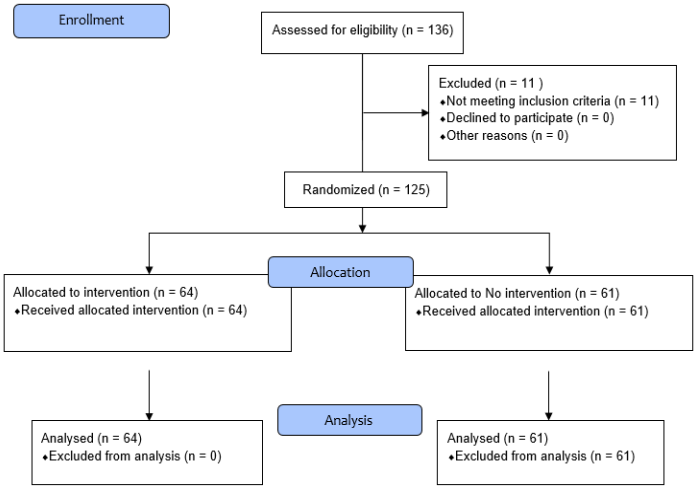
The refusal criteria

The child has a cardiac pacemaker,
There is a defect in continuity of the skin or a skin rash on the area of operation,
The health condition of the child is unstable,
The child has a deficiency in development,
The child has consumed an analgesic in the last six hours,
The child or the parent does not accept to participate in the study.

Randomization

The children were classified as VR and control group with a simple random sampling method only after taking the children's consent and written consent of the parents after giving necessary information. Children were included in the VR and control groups using the urn randomization method [28]. Two different balls, including white for the control group and red for the VR group, were placed in a black bag by the researcher. Without any knowledge of the groups, a nurse who worked there asked him to select a ball from the black bag with his eyes closed. Children were assigned to the control or experiment group according to the color of the selected ball. Thus, the children were randomly distributed into two groups (Figure 1).

Figure 1: The flow diagram of the study



Data Collection Tolls

Interview and Observation Form

This form was created based on the literature by the researchers[29-30]. The question form was sent for the examination of three experts, and it was put into the final form according to the necessary corrections. The interview and observation form is a 21-question form whose 14 questions are open-ended. The researchers collected the data from the child and parents via interviews and observation. The application time of the form is approximately 5 minutes.

Children's Fear Scale (CFS)

The scale was first introduced in 2003. This scale was developed to assess the child's fear/anxiety level. There are five different facial expressions on the scale, with no fear/anxiety on the one end and intense fear/anxiety on the other. These facial expressions were evaluated between 0 and 4. "0" stands for no fear/anxiety, and "4" stands for extreme fear/anxiety [31, 32].

Wong-Baker Faces Pain Rating Scale

The scale, which Wong and Baker developed, is suitable for the use of 3-18-year-old children. For example, the smiling face expression 0 stands for 'no pain,' while the crying face expression 10 stands for 'extreme pain' [33].

Virtual Reality (VR) Glasses

VR glasses are a method in which the patient was made to watch footage taken from a phone by approximating the lenses within a headset, used in order to isolate the patient from real life. The patients in the VR group and their parents were informed about the glasses before the operation. The VR glasses (3D VR Box 2) were placed on the eyes of the child before the circumcision operation, and he was made to watch the footage during the operation. In addition, the child was made to watch the cartoon film that he preferred through the VR headset, which was considered to attract the children. Thanks to the placement of a VR headset, the children focused on a cartoon film that they liked, and thus, they were prevented from hearing all the sounds and realizing the actions during the operation.

Timekeeper

It was used to record the duration of the crying of the child.

Data collection

The data was collected with the face-to-face interview method via the Interview and Observation Form, which was created based on the experts' opinions and in line with the literature. While assessing the children's pain and fear/anxiety levels, it was requested to evaluate the child, the parent, and two nurses to make the evaluation more objective.

The research was conducted according to the following steps: Before the data collection phase, oral and written consent were received from the parents of the children, who were selected based on the sample selection criteria. The equipment was prepared beforehand (Interview and Observation Form, VR Glasses, Timekeeper). Individual characteristics were recorded in the interview and observation form based on the interviews with the children and family members. All of the children to be circumcised were locally anesthetized before the operation, and each child waited for 10 minutes for the anesthetic substance to take effect. Then, the child and his parents were admitted to the circumcision surgery room. The child was asked to lie down on the operation table. In order to determine the preoperative fear/anxiety levels of the children both in the VR and the control groups, the Children's Fear Scale (CFS) was applied. The fear levels of the children were determined via CFS and observations of the child, parents, and two nurses. One of the parents admitted to the operation room was asked to hold the hands of the child on the head side, while the other parent was asked to hold the legs to fasten up the child; subsequently, the circumcision operation was conducted. After these procedures, the children in the control group were circumcised under normal conditions. During the routine circumcision operation, no procedures were applied to the child. As per the VR group, they were allowed to watch a cartoon film up to their choices. The children in the VR group began to watch their cartoon films via VR glasses as soon as they lay down on the table, just one minute before the operation. Thus, the child was prevented from observing the operative process around him, and he focused on the cartoon film. As soon as the children began crying, the timekeeper started and recorded the crying duration. After the circumcision operation, the fear and pain levels of the children in both groups were observed and recorded.

Statistical analysis

Statistical analyses of the study were made in SPSS 21.0 package program. Numbers, percentages, and mean values (standard deviation) were used from descriptive analyses. In the analysis of differences between groups, t-test, paired t-test, chi-square, Mann Whitney U, and Kruskal Wallis tests were used in independent groups. The significance level was accepted as $P < 0.05$.

Ethical considerations

In order to conduct the research study, ethics committee permission was obtained from "Karaman University, Faculty of Health Sciences, Ethics Committee of non-Pharmaceuticals and non-Medical Device Researches" (dated 16/06/2017 and numbered 2017/975), and institutional permission was obtained from the "Ministry of Health Karaman Public Hospitals Institution General Secretariat of the Public Hospitals Association of Karaman Province" (dated 13/07/2017, and numbered 50658796-774.99-E.3674). Additionally, written consent was obtained from all participant patients and their parents concerning their volition to participate in the study.

Results

In total, 125 children participated in the study. The distribution of the demographical features and pre-operative-pre-circumcision fear levels of the children were similar in the groups (Table 1).

There was statistically no significant difference between the groups concerning the previous hospital experiences of the children and the anesthesia used during the operation (Table 2).

Table 1: Distribution of children by demographic characteristics (n = 125)

	VR group (n = 64) Mean (SD)	Control group (n = 61) Mean (SD)	t	*P*-value
Child's age (year)	7.03 (1.41)	7.08 (1.43)	0.199	0.842
BMI	18.76 (1.99)	18.32 (1.85)	-1.236	0.219
The preoperative child's fear levels	1.03 (0.18)	1.05 (0.22)	0.508	0.614
The pre-circumcision child's fear levels				
According to the child	2.61 (1.02)	2.33 (1.22)	-1.03	0.163
According to the parent	3.34 (0.72)	3.30 (0.86)	-0.343	-0.732
According to the first observer	3.47 (0.59)	3.34 (0.77)	-1.016	0.312
According to the second observer	3.45 (0.73)	3.41 (0.78)	-0.319	0.750

Table 2: Distribution according to children's hospital experience and analgesic agent applied in circumcision (n = 125)

	VR group (n = 64)		Control group (n = 61)		χ^2	*P*-value
	n	%	n	%		
Have you been hospitalized before?						
Yes	7	10.9	9	14.8	0.408	0.523
No	57	89.1	52	85.2		
Name and dose of analgesic applied in the circumcision						
Marcaine* 3 cc, Citanest ** 3 cc	29	45.3	27	44.3	0.018	0.991
Marcaine 3 cc, Citanest 4 cc	27	42.2	26	42.6		
Marcaine 4 cc, Citanest 4 cc	8	12.5	8	13.1		

* Marcain: The active ingredient is bupivacaine hydrochloride. ** Citanest: The active ingredient is Prilocaine hydrochloride.

The mean duration of the procedure for the children in the VR group was 365.36 (64.73) seconds, while it was 538.66 (179.79) seconds in the control group. Process-induced crying time was measured as 21.31 (41.74) seconds in the VR group and 322.21 (188.86) seconds in the control group. When the duration of the procedure and the duration of crying during the procedure were evaluated, it was determined that both periods were shorter in children in the VR group. In this case, it has been observed that VR glasses shorten the processing time as well as the crying times of children. Children's post-procedural fear was evaluated by three people: the child, the parent, and the observer. According to all three evaluations, the fear score averages of the children in the VR group were significantly lower (by child VR = 0.36 (0.68), Control = 3.51 (0.67); by parents VR = 0.39 (0.70), Control = 3.48 (0.72); by observer VR = 0.38 (0.70), Control = 3.54 (0.79)) ($P < 0.001$). On the other hand, no significant difference was found between the groups in terms of pain score averages ($P > 0.05$) (Table 3).

Table 3: Distribution according to groups in terms of the duration of circumcision operation and crying of the child (n = 125)

	VR group (n = 64) Mean (SD)	Control group (n = 61) Mean (SD)	t	*P*-value
Duration of application (sec) (Min-Max)	365.36 (64.73) (254-522)	538.66 (179.79) (280-1200)	7.236	<0.001
Child's crying time (sec) (Min-Max)	21.31 (41.74) (0-190)	322.21 (188.86) (20-860)	12.434	<0.001
Child's fear after circumcision (according to the child)	0.36 (0.68)	3.51 (0.67)	26.085	<0.001
Child's fear after circumcision (according to the parent)	0.39 (0.70)	3.48 (0.72)	24.195	<0.001
Child's fear after circumcision (according to the observer)	0.38 (0.70)	3.54 (0.79)	23.770	<0.001
Pain levels after circumcision (according to the child)	0.28 (1.00)	0.56 (2.04)	0.969	0.334
Pain levels after circumcision (according to the parent)	0.22 (0.72)	0.46 (1.80)	0.986	0.326
Pain levels after circumcision (according to the observer)	0.28 (0.93)	0.46 (1.73)	0.720	0.473

Discussion

This study examined the effect of the distraction method utilizing VR glasses on the pain, fear, and anxiety that are possible to observe in the children during the circumcision operation. No statistically significant difference was determined between the VR and control groups concerning the pre-circumcision fear levels of children evaluated by the child, the parents, and the observer. This situation is an expectable result for determining the effectiveness of the VR glasses. Based on the information provided by parents and observers, we found that children in the VR group had lower anxiety depending on the postoperative situation. Although there is no similar study in the literature concerning the circumcision operation, similar results were observed in studies conducted on other invasive interventions. For example, in a randomized controlled study about the effects of VR glasses on the fear/anxiety levels during phlebotomy of 10-21-year-old children, Gold and Mahrer [34] reported that the use of VR glasses highly reduced acute interventional pain and anxiety and that both the patients and the caregivers were highly satisfied. Similar results have also been reported [26, 35].

The study also determined that the use of distraction via VR glasses reduces the duration of the operation and the crying of the child. This finding is supportive of the positive effects of the VR glasses during the circumcision operation. There are similar results in the literature. For example, Hua et al. [10] reported that the dressing change duration of the group with VR distraction was shorter than the group with standard distraction methods (such as books, toys, and television).

According to the child, parents, and the observer, no significant difference was found between the groups in terms of pain levels after circumcision. However, studies with different results were encountered in the literature. Those studies were conducted on healthy children and children being treated in other clinics such as oncology and burn units. For example, in a randomized controlled study conducted by Gerçeker et al. [36] about the effectiveness of VR glasses and external cold and vibration in reducing the pain during phlebotomy on 121 children of 7-12 age, it was determined that there was statistically no significant difference between the groups that were applied VR and external cold and vibration concerning the pain scores, however, compared to the control group, the pain scores of both groups were determined as lower. There are similar studies in the literature [27, 37-45]. The results obtained from the pain literature

and those obtained from our study differ due to the use of analgesics in this study.

Limitations

The study was limited to the 6-11 age groups only. It is recommended to evaluate the effectiveness of VR glasses for earlier circumcisions.

Conclusions

It can be stated that using distraction through VR cartoon films highly reduces the fear emerging in children during circumcision. Furthermore, it significantly decreases the duration of the operation, thus, rendering this operation no more a traumatic event for the child. It was also determined that this method did not influence the pain felt during this operation. The children display more comfortable behaviors after the operation can be attributed to the fact that circumcision is a fear-focused process rather than a pain. Accordingly, the VR method is a non-initiative, non-traumatic, and non-pharmacologic, effective method that reduces the fear and decreases the duration of the process. Therefore, it is suggested that the VR method is used during the circumcision process, particularly for children between 6-11 years old.

Clinical Implications

In circumcision, a method should be used to reduce and prevent anxiety, fear, and pain in the child. For example, having children watch cartoon movies during the circumcision operations is highly effective in reducing the fear, shortening the duration of the crying children, and conducting the procedure faster. Therefore, during circumcision, distraction through VR glasses can be applied to children between 6-11 years old. During interventional procedures in children, VR glasses are an easy-to-use, economical, safe, and practical method that will reduce or prevent fear/anxiety and pain and reduce application time.

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The effect of motor and functional independence of disabled children on musculoskeletal disorders in pediatric caregivers: A cross-sectional study

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This study was reviewed and approved by the İnönü University Clinical Research Ethics Committee (Decision number: 2020/163). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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Abstract

Background/Aim: There are conflicting results regarding the effect of motor and functional independence levels of disabled children on the burden of care. In addition, this burden, as well as musculoskeletal problems of pediatric caregivers, has not been examined in detail. The aim of this study is to examine the effects of motor and functional levels of the disabled child.

Methods: The study was planned as a single-blind, multicenter, cross-sectional study. Children between ages 1-12 with physical disabilities from various problems, and 65 caregivers over the age of 18 who cared for them for at least 6 months, were included. Caregivers were divided into two groups, as per the BAKAS Caregiver Impact Scale score as high care burden (n = 33) or low care burden (n = 32). The motor level of the disabled child was determined by the Gross Motor Function Classification System, and the functional level of the Pediatric Functional Independence Measurement. The Nordic Musculoskeletal Questionnaire was used to evaluate musculoskeletal problems in caregivers.

Results: There was no significant difference between the Gross Motor Function Classification System levels of children in groups ($P > 0.05$). The Pediatric Functional Independence Measurement scores of children in the high care burden group were significantly lower than those in the low care burden group ($P < 0.05$). According to a comparison of pain in parts of the body for 12 months, using the Nordic Musculoskeletal Questionnaire, the percentage of pain in the neck, shoulder, back, elbow, hand, hip, and foot regions of caregivers was significantly higher in the group with a high care burden ($P < 0.05$). There was no significant difference between percent of low back and knee pain in the last 12 months ($P > 0.05$). A weak positive correlation was found between the BAKAS Caregiver Impact scores and the Pediatric Functional Independence Measurement of children with disabilities ($r = 0.26$; $P = 0.03$).

Conclusion: The lower functional level of the disabled child may cause an increase in caregiver burden of both the caregivers and musculoskeletal disorders.

Keywords: Caregivers, Caregiver burden, Disabled child, Musculoskeletal pain

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Introduction

Disability is a situation that limits or prevents activities by gender, age, social, and cultural situation of the individual due to damage or disability [1]. The rate of disability is increasing gradually with congenital anomalies, increased survival rate in preterm births, and some genetic disorders [2]. Disability can be seen separately or combined as psychological, physical, developmental, and mental problems. According to the World Health Organization, it is estimated that 5.1 percent of children aged 0-14 (approximately 93 million children) have a disability and 0.7 percent [approximately 13 million children] have a serious disability [3]. Approximately 12% of 6.6 million children in the US have a disability [4].

It is also estimated that there are approximately 9 million children with special needs or disabilities between the ages of 0-18 in Turkey. This highlights that there is 1 disabled child or adult in every 7 to 8 families [5]. The family who learns their child is disabled or the family whose child has a disability after birth experiences profound grief. Families may go through many negative psychological processes such as denial, anger, crisis, depression, and shame [6]. Families are obliged to care for their disabled children physically, socially, emotionally, and financially – and as such, this situation creates a burden of care due to difficulties experienced in the care process, feeling under stress, or under a burden [7]. It creates many psychological and physical problems for the caregivers [8]: studies report that they have psychological health conditions, e.g., high stress and depression [9]. The caregiver undertakes physically demanding tasks, like assisting with the child's transfers and personal needs [10].

Within the scope of these interventions, a change from normal posture causes biomechanically incorrect positions. The prolonged caregiving period and worsening of the motor level of the disabled children cause fatigue, headache, and back pain, i.e., low back pain [11]. It was found that 84% of caregivers of neurological patients have physical problems themselves [12]. Despite this, few studies have addressed the effects of care burden on quality of life in the caregivers for children with disabilities. When studies are assessed, they relate to difficulties experienced by the families and related psychological factors [13-15].

Towards this goal, our aim was to examine the effects of motor and functional level of the disabled child on care burden and musculoskeletal system disorders in pediatric caregivers.

Materials and methods

This study is a multicenter, cross-sectional study, which was reviewed and approved by the Inonu University Clinical Research Ethics Committee (Decision No. 2020/163); this study was conducted according to the principles of the Declaration of Helsinki. Informed consent was obtained from the parents of participants before the study started.

Research data were collected between 6 July and 6 August 2020. Children aged 1-12 years with physical disabilities and caregivers over the age of 18 who took care of them for at least 6 months were included in this study. Individuals in institutions were selected by the non-probability random sampling method, as caregivers with a musculoskeletal injury or surgery linked to their musculoskeletal system in the last 6 months, or who had low back-back-neck pain due to rheumatological diseases were excluded from the study.

Private hospitals and special education centers were chosen by drawing lots among 33 centers (special education and rehabilitation centers, physical therapy centers, and private hospitals) in the city center of Malatya, for rehabilitation services by the independent researcher. This research consisted of disabled children and their families who had applied for assistance. Demographic variables of all participants (the disabled child and caregiver), including age, gender, weight, and height, were recorded. In addition, caregivers were asked about their employment status, how long they had been working, and whether they engaged in exercise. The burden of caregivers was evaluated with the Bakas Caregiver Impact Scale, which consists of 15 questions with scores between +3 (best possible score) and -3 (worst possible score). A lower score can occur with a negative change, while a higher score can occur with a positive change [16, 17]. This impact scale was conducted through face-to-face interviews with caregivers. The median score was calculated to be 55, so individuals over 55 constituted the group with low care burden (n = 32) and those below that had a high care burden (n = 33).

The mobility and functional level of the disabled child was determined according to the Gross Motor Function Classification System (GMFCS). This system offers age-appropriate scoring between 1-5. Level 1 allows ambulation indoors and outdoors without the need for assistive devices, while level 5 is defined as completely dependent in terms of mobility [18, 19].

The Pediatric Functional Independence Scale (WeeFIM) was used to assess the level of functional independence of those with disabilities between 6 months and 21 years of age. This scale consists of a total of 18 items that evaluate 3 areas: self-care, mobility, and cognitive function. Scores ranged between 1 and 7 points for each item, with 7 points indicating activities performed by the disabled individual independently, and 1 indicating activities that had to be done with full assistance [20, 21]. Their status for sub-parameters of the WeeFIM was evaluated in conjunction with information from the physiotherapist and caregiver.

The Nordic Musculoskeletal Questionnaire was used to evaluate musculoskeletal problems in caregivers: it included 27 items to assess the presence of musculoskeletal symptoms over a 12-month period, covering nine different parts of the body (neck, shoulders, elbows, hands/wrists, back, waist, hips/thighs, knees, and ankles). All answers were based on a binary "yes/no" answer [22]. In this study, part of the questionnaire related to the presence of pain, suffering, and discomfort in the last 12 months in 9 body regions.

Statistical analysis

The Shapiro-Wilk test was used to assess normality of the data. Descriptive statistics (frequency, mean, standard deviation) were applied to characterize individuals within groups. Differences between two groups were compared with the Independent Sample T-test (normally distributed variables) and

the Mann-Whitney U test (for non-normally distributed variables). Categorical variables were evaluated with the Chi-squared test. The relationship between the BAKAS Caregiver Impact scores and the WeeFIM scores of children with disabilities was evaluated with Spearman's correlation test (parameters that do not show normal distribution). Correlation values ≥ 0.4 were considered satisfactory (r ≥ 0.81–1.0 excellent, 0.61–0.80 very good, 0.41–0.60 good, 0.21–0.40 fair, and 0.00–0.20 poor). The significance level was set at $P < 0.05$. Statistical analysis was performed with SPSS software v. 25.0. Power analysis was performed before starting the study with $\alpha = 0.05$ and 1-β (power) = 0.80. Considering that the prevalence of disabled individuals in society is 12.3% (39%), it was calculated that at least 63 people should be included in this research. The public statistical software OpenEpi, v. 3 (http://www.openepi.com) was used to calculate the sample size.

Results

At the end of the study period, 69 disabled children and caregivers were included, but four individuals who filled in evaluation forms incompletely were excluded. A total of 65 individuals, 33 individuals in the high care burden group and 32 individuals in the low care burden group, were included in our analysis. The characteristics of both groups are examined in Table 1. Groups were similar in terms of age, gender, and body mass index of caregivers ($P > 0.05$), and were also similar in terms of the ages of disabled children ($P > 0.05$). However, the body mass index was higher in the group with a high care burden ($P < 0.05$), but in groups with high and low care burdens, 9.1% and 21.9% of caregivers engaged in exercise activities, respectively. There was no difference between the groups' duration of care and the working status of caregivers ($P > 0.05$).

Table 1: Characteristics of caregivers and children with disabilities

	High Care Burden (n = 33) Mean (SD)	Low Care Burden (n = 32) Mean (SD)	*P*-value
Caregiver Age, year	34.90 (7.31)	36.96 (7.48)	0.26[a]
Caregiver BMI, kg/m²	27.14 (3.41)	26.81 (5.54)	0.77[a]
	Median (min/max)	Median (min/max)	
Child Age, year	4.0 (1/12)	5.0 (1/12)	0.09[b]
Child BMI, kg/m²	(10.94/38.78)	15.86 (9.17/23.44)	0.03[b]
	n (%)	n (%)	
Caregiver Sex			
Female	30 (90.9)	30 (93.75)	1.00[c]
Male	3 (9.1)	2 (6.25)	
Exercise Habits			0.18[c]
Yes	3 (9.1)	7 (21.9)	
No	30 (90.9)	25 (78.1)	
Care Time			0.26[c]
6 months-4 years	23 (69.7)	18 (56.3)	
5 years and above	10 (30.3)	14 (43.8)	
Working status			0.47[c]
Yes	6 (18.2)	3 (9.4)	
No	27 (81.8)	29 (90.6)	

BMI: body mass index, SD: standard deviation, [a] Independent Sample T-test, [b] Mann-Whitney U test, [c] Chi-squared test

Comparison of WeeFIM scores, GMFCS levels, and the Nordic Musculoskeletal Questionnaire for children with disabilities in groups with high and low care burden, is shown in Table 2. The WeeFIM scores of children with high care burden were significantly lower than the group with low care burden ($P < 0.05$). Yet, there was no significant difference between the GMFCS levels of disabled children in groups ($P > 0.05$). In comparison to pain in different parts of the body over the last 12 months, while using the Nordic Musculoskeletal Questionnaire, the percent of pain in the neck, shoulder, back, elbow, hand, hip, and foot regions of the caregivers was found to be significantly higher in those with a high care burden ($P < 0.05$). There was no significant difference between groups with low back and knee pain over the last 12 months ($P > 0.05$). There was a weak positive correlation between the BAKAS Caregiver Impact scores of caregivers without grouping and the WeeFIM scores of children with disabilities (r = 0.26; $P = 0.03$).

Table 2: Comparison of participants' functional independence, motor level, and musculoskeletal problems according to care burden

		High care burden (n = 33)	Low care burden (n = 32)	*P*-value
WeeFIM, Median		29 (12/116)	40 (18/119)	0.03[a]
GMFCS		n (%)	n (%)	0.90[b]
Level I- III		15 (45.5)	15 (46.9)	
Level IV- V		18 (54.5)	17 (53.1)	
NORDIC				
Neck	Yes	17 (51.5)	7 (21.9)	0.01[b]
	No	16 (48.5)	25 (78.1)	
Shoulder	Yes	14 (42.4)	6 (18.8)	0.03[b]
	No	19 (57.6)	26 (81.3)	
Back	Yes	22 (66.7)	6 (18.8)	0.00[b]
	No	11 (33.3)	26 (81.3)	
Elbow	Yes	8 (24.2)	1 (3.1)	0.02[b]
	No	25 (75.8)	31 (96.9)	
Hand	Yes	19 (57.6)	7 (21.9)	0.00[b]
	No	14 (42.4)	25 (78.1)	
Waist	Yes	24 (72.7)	17 (53.1)	0.10[b]
	No	9 (27.3)	15 (46.9)	
Hips/Thighs	Yes	9 (27.3)	2 (6.3)	0.02[b]
	No	24 (72.7)	30 (93.8)	
Knee	Yes	13 (39.4)	7 (21.9)	0.12[b]
	No	20 (60.6)	25 (78.1)	
Ankle	Yes	7 (21.2)	1 (3.1)	0.05[b]
	No	26 (78.8)	31 (96.9)	

WeeFIM: Pediatric Functional Independence Scale, GMFCS: Gross Motor Function Classification System, [a] Mann-Whitney U test, [b] Chi-squared test

Discussion

In this study, effects of the motor and functional level of the disabled child on burden of care and musculoskeletal disorders in pediatric caregivers were assessed. Results showed that functional levels of disabled children with a high burden of care were lower, but their motor levels were similar. Moreover, it was found that those with a high care burden had more musculoskeletal disorders.

The functional level of children is one of the most important factors affecting burden of care. As the level of independence increases, the need for caregivers decreases. Henry et al. [23] reported that as the level of independence decreased for caregivers, back pain increased and their mood was negatively affected; accordingly, physical functionality of the caregiver decreased. Similarly, Rigby et al. [24] observed changes in the burden of caregivers between onset and the first year of taking care of stroke patients, and found that as the level of functional disability increased, the burden of care also increased. The pediatric functional independence scale was used to determine function levels, and it was found that the burden of care decreased as functional independence increased, akin to other studies in the literature.

Until now, the psychological traits of caregivers for those with disabilities, and changes that occurred in the caregiving process, were extensively researched [25]. When the studies are examined, care burden for many diseases such as stroke, cerebral palsy, and autism spectrum disorder were examined, with a positive relationship observed between care burden, depression, and anxiety [26-28]. Kavlak et al. [29] found that caregivers of children with cerebral palsy had a high burden of care, but no significant relationship was found between gross motor function level and caregiver burden. Özden et al. [28] showed there is a highly significant relationship between

spasticity levels of children with cerebral palsy and burden of care, but no significant relationship was established between levels of gross motor function and burden of care. In our study, there was no significant relationship between care burden and gross motor level of the child, which strongly coincides with the literature.

In our study, it was observed that more women had the responsibility of caregiving in the family. As such, since individuals who care for disabled children must stand in a flexed posture for long periods to lift them and meet their needs for a transfer, it was observed that they experienced problems when the load was more exposed, such as the waist, back, and wrist. The physical health of caregivers was assessed with different methods, including computer-assisted sensor dosimetry, three-dimensional postural exam, video recording, and the Nordic Musculoskeletal Assessment [30-33]. In our study, pain levels were higher in the neck, shoulder, back, elbow, hand, hip, and foot, in line with the literature, to evaluate the musculoskeletal system [10]. The percent of pain in caregivers' lumbar region was higher in the group with a high burden of care, but was not significant. Since low back pain is seen as a common problem in our society, it reduces the difference between the groups.

Limitations

Our study has some limitations, which is related to the number of samples. Scanning with larger samples would yield more generalizable results. Since pain status over the last year was evaluated, it could affect generalizability of the results. Prospective, longer-term follow-up studies may be useful in assessing the effect of caregiving on isolated musculoskeletal disorders. The low exercise activities in the groups prevented understanding the effect of exercise on preventing musculoskeletal problems.

Conclusions

As a result, our study will make significant contributions to a limited number of literature reports that evaluate children's motor and independence levels on caregivers' musculoskeletal problems. It was shown that the functional level of a disabled child is related to the burden of care for the caregiver and functional level of the disabled child – which relates to musculoskeletal disorders. Our results show that caregivers can have severe problems in terms of musculoskeletal disorders. Raising awareness for caregivers and explaining appropriate ergonomics would be effective in preventing musculoskeletal disorders.

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Age, body mass index, and diabetes mellitus are associated with an increased risk of acute kidney injury after coronary surgery: Retrospective cohort study

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Ethics Committee Approval
The study was approved by the Ankara City Hospital 1° Ethics Committee (E1-22-2572, 20.04.2022).
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Abstract

Background/Aim: Cardiac surgery-associated acute kidney injury (CSA-AKI) is a significant complication of cardiac surgery and is associated with increased morbidity and mortality. Identifying risk factors can help clinicians alleviate the risk of developing CSA-AKI and associated complications. Therefore, this study aimed to identify pre-operative patient-related risk factors of CSA-AKI in patients undergoing coronary surgery.

Methods: The current study was a single-center retrospective cohort study of adult patients undergoing coronary surgery with cardiopulmonary bypass (CPB) over an 8-month period. AKI was scored according to The Kidney Disease Improving Global Outcomes (KDIGO) scoring system. Patients' age, gender, body mass index (BMI), comorbidities, KDIGO staging in AKI patients, and 30-day mortality rates were recorded. These variables were compared between AKI(−) and AKI (+) groups. Univariate binary regression analysis was performed between the variables that had statistically significant differences and AKI.

Results: A total of 248 coronary surgery patients were analyzed. The overall incidence of CSA-AKI was 16.5%. Age, BMI, and the proportion of diabetic patients were significantly higher in the AKI (+) group (P = 0.04, P < 0.001, and P = 0.022, respectively). The proportion of gender, chronic obstructive pulmonary disease (COPD), hypertension (HT), baseline creatinine levels, aortic cross-clamping, cardiopulmonary bypass (CPB), total operation duration, and 30-day mortality were similar between the groups. Univariate analysis demonstrated that CSA-AKI was significantly associated with age ≥ 65 years (odds ratio [OR] = 2.506; confidence interval [CI]: 1.265–4.967; P = 0.008), BMI of ≥ 25 kg m^{-2} (OR = 8.994; CI: 1.199–67.980; P = 0.033), and diabetes mellitus (OR = 2.171; CI: 1.103–4.273; P = 0.025).

Conclusion: The current study revealed that patients with increased age, BMI, and DM had a higher incidence of CSA-AKI. Therefore, even though these patient-related variables are known as non-modifiable parameters, more attention should be paid to preventing CSA-AKI during peri-operative management of these patients.

Keywords: Cardiac surgery, Acute kidney injury, BMI, Obesity, Diabetes mellitus, Age

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Introduction

Cardiac surgery-associated acute kidney injury (CSA-AKI) is the most common major complication of cardiac surgery and has an incidence ranging from 7% to 40% [1]. The severity of CSA-AKI varies from asymptomatic increases in creatinine levels to the requirement for renal replacement therapies, which significantly affect intensive care unit (ICU) and hospital lengths of stay and mortality. Severe CSA-AKI causes a 3–8‑ fold higher peri-operative mortality and prolonged length of stay in the ICU and hospital [2]. Furthermore, the risk of mortality remains high for years regardless of other risk factors even in patients with complete renal recovery.

Identifying risk factors could help clinicians alleviate the risk of CSA-AKI and CSA-AKI-associated complications [3]. Current research has found many components related to CSA-AKI, and these factors are multifactorial, interrelated, and mostly synergistic. The development of CSA-AKI mainly occurs in older, sicker patients who undergo more complex surgeries. However, patients without these risk factors can still develop CSA-AKI [4].

This study focuses on patient-related factors affecting AKI in coronary surgery patients. In line with this objective, AKI was evaluated in patients who had undergone coronary surgery, and the relationship between AKI and pre-operative variables was compared.

Materials and methods

The current study was a retrospective cohort study of patients who underwent coronary surgery with cardiopulmonary bypass (CPB) between June 2021 and April 2022. It was approved by the Ankara City Hospital 1° Ethics Committee (E1-22-2572, 20.04.22). A total of 248 eligible adult patients were included in the final analysis. The number of coronary surgery cases in our hospital during the study period determined the sample size. The exclusion criteria included patients under 18 years of age, pre-operative kidney injury, emergency cases, repeat surgeries, and/or a lack of clinical data. The pre- and post-operative patient data were obtained from the electronic database of the hospital, intra- and post-operative anesthesia records, and ICU follow-charts.

AKI was divided into three stages: (1) Stage I, an increase in serum creatinine by ≥ 0.3 mg/dL within 48 h or an increase in serum creatinine of 1.5–1.9 times the value at baseline; (2) Stage II, an increase in serum creatinine levels 2.0-2.0 times the value at baseline; and (3) Stage III, an increase in serum creatinine levels of 3.0 times the value at baseline, an increase in serum creatinine to ≥ 4 mg/dL, and/or initiation of renal replacement therapy as defined by The Kidney Disease Improving Global Outcomes (KDIGO) [5].

All patients received balanced anesthesia using our routine clinical protocols. Standard CPB was established, and antegrade cold blood cardioplegia was used for myocardial protection. Hemoglobin concentrations were kept above 7.5 g dl^{-1} during CPB and above 8.5 g dl^{-1} after CPB. All patients were transferred to the ICU after surgery.

Patients' ages, genders, body mass index (BMI) values, comorbidities, such as diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD) and/or hypertension (HT), total operation, CPB, and aortic cross-clamping duration, pre- and post-operative creatinine levels, KDIGO staging in AKI patients, and 30-day mortality rates were recorded. According to AKI development, patients were divided into AKI (−) and AKI (+) groups.

Statistical analysis

Statistical analyses were performed using IBM SPSS for Windows (IBM Corp., version 22.0, Armonk, NY, USA). Kolmogorov-Smirnov test was utilized to determine the distribution of data. Baseline data were expressed as mean (standard deviation), median (IQR 25-75), or number (percentage) as appropriate. The chi-squared test was used for the independent samples with categorical variable. An independent t-test was used for normally distributed variables, and Mann–Whitney U test was used for variables that were not normally distributed. Univariate binary regression analysis was performed to determine the relationship between the variables that had statistically significant differences and CSA-AKI. Univariate regression analysis was performed by categorizing the numerical data that were not normally distributed and statistically different between the groups. A P-value < 0.05 based on two-sided tests was considered statistically significant.

Results

A total of 248 patients were enrolled, of which 200 (80.6%) were male. The median age was 60 (55–66) years. Ninety-four (37.9%) patients had DM, 15(6%) had COPD) and 170 (68.5%) of them had HT. The median BMI was 27 (25–30). The overall incidence of CSA-AKI was 16.5% (41/248). The incidence of AKI stage I was 14.5%, stage II 2%, and stage III 0% according to the AKI diagnosis criteria of KDIGO (Table 1).

Table 1: Peri-operative variables of all study population

	Value
Age (years)	60 (55–66) *
Male sex	200 (80.6%) †
Diabetes mellitus	94 (37.9%) †
Chronic obstructive pulmonary disease	15 (6%) †
Hypertension	170 (68.5%) †
BMI (kg/m^2)	27 (25–30) *
Total operation duration (min)	270 (240–313) *
CPB duration (min)	100 (84-124) *
CC duration (min)	69 (25) Ψ
Preoperative creatinine	0.86 (0.77–1.01) *
Postoperative acute kidney injury	41 (16.5%) †
• KDIGO stage I	36 (14.5%) †
• KDIGO stage II	5 (2%) †
• KDIGO stage III	0 †
30-days mortality	4 (1.6%) †

* Median (interquartile range [IQR] 25%–75%); †: n (%); Ψ: Mean (standard deviation [SD]); BMI: Body Mass Index; CPB: Cardiopulmonary Bypass; CC: Cross-clamping; KDIGO: Kidney Disease Improving Global Outcome.

The proportion of gender, COPD, HT, baseline creatinine, aortic cross-clamping, CPB, and total operation duration, postoperative drainage, and 30-day mortality rates were similar between the groups. Age, BMI, and the proportion of diabetic patients were significantly higher in the AKI (+) group (P = 0.04, P < 0.001, and P = 0.022, respectively) as shown in Table 2.

Since they were not distributed normally, age was categorized as < 65 and ≥ 65, and BMI was categorized as < 25 and ≥ 25 to use these parameters in the univariate binary logistic regression analysis. Univariate analysis demonstrated that CSA-AKI was significantly associated with age ≥ 65 years (odds ratio [OR] = 2.506; confidence interval [CI]: 1.265–4.967; P = 0.008),

BMI ≥ 25 kg m^{-2} (OR = 8.994; CI: 1.199–67.980; P = 0.033), and DM (OR = 2.171; CI: 1.103–4.273; P = 0.025) as shown in Table 3.

Table 2: Peri-operative variables of two groups

Variables	AKI (–) group n = 207	AKI (+) group n = 41	*P*-value
Age (years)	59 (54–65)	64 (58–72)	0.004*
Age ≥ 65	57 (27.5%)	20 (48.8%)	0.007Ψ
Male Gender	165 (79%)	35 (87%)	0.686Ψ
BMI (kg/m^2)	27 (25–27)	30 (28–32)	< 0.001*
BMI ≥ 25	169 (81.6%)	40 (97.6%)	0.011Ψ
Diabetes Mellitus	72 (34%)	22 (53%)	0.022Ψ
Hypertension	31 (14%)	9 (21%)	0.152Ψ
Chronic Obstructive Pulmonary Disease	13 (6%)	2 (5%)	0.731Ψ
Total Operation Duration (min)	270 (240–310)	278 (240–310)	0.468*
Cardiopulmonary Bypass Duration (min)	98 (83–121)	101 (88–128)	0.379*
Aortic Cross-Clamping Duration (min)	67 (25)	71 (24)	0.382†
Postoperative Drainage (ml)	650 (500–850)	600 (450–750)	0.324*
Preoperative Creatinine (mg/dl)	0.86 (0.77–1)	0.86 (0.78–1.06)	0.878*
30-day Mortality	2 (0.9%)	2 (4%)	0.069Ψ

BMI: Body Mass Index; *: Mann–Whitney U Test, Ψ: Chi-Squared Test, †: Independent Samples T-Test

Table 3: Univariate predictors of CSA-AKI

Variables	*P*-value	OR	95% CI
Age ≥ 65 (years)	0.008	2.506	1.265–4.967
BMI ≥ 25 (kg/m^2)	0.033	8.994	1.199–67.480
Diabetes Mellitus	0.025	2.171	1.103–4.273

OR: Odds Ratio, CI: Confidence Interval, BMI: Body Mass Index

Discussion

In this study, the overall incidence of CSA-AKI was 16.5%, which is in accordance with previous studies in the literature [2, 4]. Older age, DMI , and higher BMI were associated with an increased risk of developing CSA-AKI.

Standardizing the definition of AKI has advantages for diagnosing and staging. Although many novel biomarkers have been shown to be effective in detecting AKI, creatinine is nonetheless still the gold standard. The KDIGO consensus definition of AKI describes stage 1 AKI as an increase of 0.3 mg/dL creatinine within 48 h or an increase of 1.5 times the baseline value over seven days with the subsequent stages representing more severe kidney injury [5]. Patients who have had cardiac surgery in the past seven days and meet the KDIGO criteria for AKI can be said to have CSA-AKI.

Many studies have revealed several components of injury related to CSA-AKI. These components can be active at various stages of surgery with different intensities. The primary injury factors are hemodynamic and metabolic, ischemia–reperfusion injury, oxidative stress, inflammation, toxins, microembolization, and/or neurohormonal activation [6]. Risk factors can be classified as patient-related, operation-related, and physiological. It is generally suggested that operative risk factors (surgical complexity, CPB, aortic cross-clamping, operation duration, and low hematocrit during CPB) and physiological risk factors (hypotension, hypovolemia, blood transfusion) are commonly modifiable, procedure-related, and potentially preventable. It has been shown that shortening the duration of CPB and aortic cross-clamping, preventing hypotension, low hematocrit levels, and also blood transfusions are cornerstones for preventing CSA-AKI [1]. In contrast, patient-related factors (age, gender, smoking, obesity, and/or comorbidities) are considered non-modifiable factors. However, some patient-related factors, such as cessation of smoking, lowering one's BMI, and well controlled blood glucose and blood pressure levels may be modifiable in the long-term in cardiac patients. As Kunt et al. [7] reported, metabolic syndrome, which is defined as the coexistence of hyperglycemia, dyslipidemia, abdominal obesity, and HT, seems to be associated with an increased incidence of AKI after cardiac surgery. Moreover, it is suggested that it can be modifiable risk factor if its components are well-controlled.

Normal renal function decreases after the mid-30s. Consequently, the incidence of AKI increases with increasing age. However, patients over the age of 65 are more susceptible to AKI development. It is suggested that creatinine clearance and glomerular filtration rates decrease with increasing age [8]. Four main reasons for renal deterioration in elderly patients have been defined: (1) structural and functional deterioration of the kidneys associated with the aging process, (2) decreased renal reserve, (3) the presence of comorbidities, and (4) decreased ability to recover from surgery or injuries [9]. In our study population, AKI (+) patients were older than AKI (-) patients as found in other studies [10–12].

DM is another well-known risk factor for developing diabetic nephropathy and kidney injury. Several interrelated mechanisms have been suggested for how hyperglycemia exacerbates kidney injury [11]. Hyperglycemia can increase oxidative stress, augment ischemia-reperfusion injury, and induce endothelial dysfunction [13, 14]. Hyperglycemia can also cause cellular glucose overload (which generates mitochondrial dysfunction) and also increase inflammatory cytokines, thereby aggravating kidney injury [15, 16]. In the present study, diabetic patients had higher AKI incidences than non-diabetic patients. In a similar study, Wang et al. [11] investigated the association between DM and AKI in coronary surgery patients and found that diabetic patients were associated with an increased risk of AKI, which was independent of baseline renal and cardiac function. Another study reported by Hertzberg et al. [17] also reported the same results in which diabetic patients had a higher incidence of AKI after coronary surgery.

It is generally suggested that obesity causes an increase in oxidative stress, endothelial dysfunction, and inflammation. The markers of these pathological processes, including F_2-isoprostanes, interleukin 6 (IL-6), and plasminogen activator inhibitor-1, were shown to be associated with obesity [18, 19]. Moreover, their increases have also been shown in cardiac surgery [20]. Billings et al. [21] reported that BMI is an independent risk factor for CSA-AKI. Furthermore, these authors suggested that the relationship between obesity and CSA-AKI can partially be attributed to the effect of obesity on oxidative stress. Kumar et al. [22] also showed that obese patients (BMI > 40) had a higher risk of CSA-AKI than patients with lower BMI. They suggested that through secreted hormones and cytokines, visceral adipose tissue can cause inappropriate activation of the renin–angiotensin–aldosterone system and an increase in oxidative stress. Likewise, obese patients demonstrate an increase in renal plasma flow and glomerular filtration rate, thereby facilitating glomerular capillary hypertension [23]. The current study revealed that patients who developed CSA-AKI, even though they were not morbidly obese, still had a high BMI.

Limitations

This study has some limitations. First, this retrospective, non-randomized register study with a relatively small study population over eight months on patients undergoing coronary

surgery was subject to selection bias. Studies on AKI usually compare surgical techniques, anesthesia, and/or CPB management techniques. However, this study population underwent the same coronary surgery technique, anesthesia, fluid, and CPB management and had similar durations of CPB and aortic cross-clamping, which may have affected CSA-AKI incidence. Therefore, this study provided a more comparable population to determine patient-related factors in terms of CSA-AKI development.

Second, the authors did not perform long-term follow-up; only hospital stay complications were analyzed. Therefore, the long-term risk of CSA-AKI could not be discussed. In addition, serum creatinine was the only parameters used to classify CSA-AKI (rather than urine output). Because urine output is affected by several factors and is usually inadequately recorded, for these reasons, several authors only use serum creatinine to diagnose AKI [10, 24].

Conclusions

The pathophysiology of CSA-AKI seems to be intricate and associated with several risk factors, presenting notable heterogeneity in cardiac surgery patients, especially surgeries performed with CPB. The current study revealed that patients with increased age, increased BMI, and DM had higher incidences of CSA-AKI. Even though these patient- related variables are counted as non-modifiable parameters of CSA-AKI, cardiac patients should be encouraged to lower BMI and regulate blood sugar levels for the long-term duration. Besides, considering that these patients may have a higher risk of CSA-AKI, more attention should be paid to peri-operative modifiable risk factors during cardiac surgery management. These results may encourage further studies for insight into the role of patient-related risk factors in AKI in cardiac surgery patients.

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Assessment of disease activity with simplified joint ultrasonography method in rheumatoid arthritis patients

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Ethics Committee Approval
The study was approved by ethics committee of Uludag University Faculty of Medicine, Turkey (Approval date and Decision no: 19/12/2013: 2013-19/12).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
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Abstract

Background/Aim: Ultrasound (US) is a highly useful tool for assessing the disease activity of rheumatoid arthritis (RA). On the other hand, examining all joints could be time-consuming and unfeasible. Defining the number of joints and which joints should be tested is essential to accurately measuring RA activity. Several simplified US methods are undergoing development for this purpose. The aim of this study was to assess the correlation between simplified 12-joint US findings and physical examination findings/disease activity in RA patients.

Methods: This cohort study included 62 RA patients who had been undergoing treatment for at least three months. Multiplanar grayscale images and power Doppler (PD) of the 12 joints (bilateral elbow, wrist, second and third metacarpophalangeal [MCP] joints, knee, and ankle) were acquired and compared with clinical assessments. Disease activity was assessed using the clinical disease activity and simplified disease activity indices and disease activity score-28 (CDAI, SDAI, and DAS28, respectively). Synovial effusion, synovial proliferation, and PD US scores were calculated for 12 joints. Correlations between US scores and disease activity, clinical examination, and acute phase reactants were assessed.

Results: The number of joints with PD activity and US total and US synovial proliferation scores showed weak correlations with clinical activity scores (r = 0.25, r = 0.26, and r = 0.28 for SDAI and r = 0.23, r = 0.26, and r = 0.28 for DAS28, respectively). The CDAI did not present any statistically significant correlations. The agreement between US findings and clinical joint examination was generally weak. PD activities of the second MCP joints (r = 0.84, $P < 0.01$) and knees (r = 0.42, $P < 0.01$) mostly correlated with clinical examination although it was weakly correlated at the third MCP (r = 0.152) and wrist (r = 0.148), and not correlated at the elbow (r = 0.125).

Conclusion: The weak correlation between US findings and clinical examination/disease activity suggests that clinical examination alone may not be sufficient to determine joint inflammation and disease activity. US could provide a more accurate assessment of RA patients and aid in medication selection.

Keywords: Disease activity, Rheumatoid arthritis, Ultrasound

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Introduction

Rheumatoid arthritis (RA) can cause erosive joint destruction and severe loss of joint function if not treated properly [1]. Early diagnosis and treatment of the disease is important because greater inflammatory activity is observed during the first years of RA [2]. Disease remission is now an achievable target due to advances in biological treatments and tight control strategies [3]. Regular and sensitive disease monitoring is required to effectively control symptoms and accurately assess synovial inflammation to attain this goal [4]. Currently, in terms of disease activity and treatment response evaluations in RA patients, composite clinical disease activity indices are used, which include some subjective clinical variables, such as joint tenderness and patient and physician global assessments of the disease [5–7]. In general, these indices are useful in assessing patients' global disease activity, but assessment of joint tenderness and swelling based on clinical examination may not be sensitive enough to accurately guide anti-rheumatic treatments because they cannot directly measure inflammation [8].

With recent advancements in medical treatment for RA and changes in treatment goals, a greater need for more reliable monitoring methods exists, and ultrasound (US) appears to be a promising monitoring tool for addressing this need [9–11]. Evaluation with US is more time-consuming than clinical joint examination. This process makes it more difficult for every patient to routinely obtain an US scan in clinical settings. In clinical practice, evaluating all accessible joints could take a long time, making it difficult to administer. As a result, many researchers have developed a simplified US score to expedite US evaluation and improve reliability and validity during treatment follow-up [12–14]. Simplified US procedures have been shown to be valid and reliable for assessing disease activity and inflammation [12–15]. However, no agreement on which joints should be assessed in RA imaging and how many joints should be tested to correctly define disease activity can be found [13, 16–18].

This study aimed to assess the correlation between clinical joint examination, disease activity indices, and US findings in RA patients and determine the degree of correlation between different joints based on the simplified 12-joint scoring method described by Naredo et al. [13].

Materials and methods

Study protocol

The study included 62 patients who presented to the Uludag University Rheumatology outpatient clinic between December 2013 and April 2014 and were diagnosed with RA according to the 1987 American Rheumatism Association and 2010 American Rheumatism Association criteria. Patients must have been receiving medication for at least three months. The study was approved by the local Ethics Committee of Uludag University, Turkey (Approval date and Decision no: 19/12/2013: 2013-19/12). The purpose and scope of the study were explained to participants, and the informed consent form was signed.

Clinical and laboratory evaluation

Demographic and clinical patient data, such as gender, age, disease duration, duration of morning stiffness, and medications used to treat rheumatoid arthritis were collected. C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) values over the last week were recorded. Swelling and tenderness in 28 joints (bilateral elbow, shoulder, wrist, metacarpophalangeal [MCP] and proximal interphalangeal joints, and knees) were identified after clinical examination. The disease activity was measured using the clinical disease activity and simplified disease activity indices and disease activity score 28 (CDAI, SDAI, and DAS28, respectively). Health assessment questionnaire (HAQ) scores of the patients were also calculated.

Ultrasonographic evaluation

The US evaluations were performed by a single investigator blinded to the clinical and laboratory findings of the patients. Following the clinical examination and evaluation of the patients, grayscale and power Doppler (PD) US evaluation of 12 joints (bilateral second and third MCP joints, wrist, elbow, knees, and ankles) were performed on the same day. Ultrasound was performed with the MyLab60 (Esaote, Genova, Italy) US device with a 6–18 MHz multi-frequency linear probe. Multiplanar grayscale (B-Mode) and PD images of 744 joints were obtained. US evaluation was based on the simplified 12-joint scoring method described by Naredo et al. [13] and 24 synovial areas in 12 joints, including anterior and posterior recesses of the elbow, dorsal carpal recess of the wrist, dorsal and palmar sides of the second and third MCP joints, suprapatellar and lateral parapatellar recess of the knee, anterior tibiotalar recess of the ankle, and medial and lateral tendon sheaths, were evaluated.

The Outcome Measures in Rheumatology (OMERACT) definitions were used to assess synovial hypertrophy, effusion, joint erosion, and the presence of PD signals in each joint [19]. The highest score (from 0 to 3) for effusion, synovial hypertrophy, and/or PD in any synovial area of each joint was accepted as the joint's synovial effusion/proliferation and PD score. For 12 joints, the US-synovial effusion score (US-SE), US-synovial proliferation score (US-SP), and US-power Doppler score (US-PD) ranging from 0 to 36 were calculated. The total US score (USTotal) was calculated by adding the effusion, synovial proliferation, and PD US scores from 12 joints (ranging from 0 to 108). For each patient, the number of joints with synovial effusion (SE-JC), synovial proliferation (SP-JC), and PD signal (PD-JC) were counted. Pathological synovitis was defined as a grayscale and/or a PD US signal score ≥ 1.

Statistical analysis

A Kendall's W value of < 0.40 was considered a weak correlation, 0.40–0.69 a moderate correlation, 0.70–0.89 a high correlation, and 0.90–1.00 a very strong correlation. As a result, correlation coefficients of at least ≥ 0.4 in US parameters were considered significant. The sample size was at least 47 when the Type I error was set at 0.05, and the confidence interval was 80%. Sixty-two patients were enrolled in this study.

Statistical analysis was performed with SPPS version 22.0 (Chicago, IL, USA) software. Quantitative variables, such as gender, age, disease duration, DAS28, SDAI, and CDAI were given as descriptive statistics (mean, standard deviation,

maximum–minimum values). The Kolmogorov–Smirnov test was used to assess the normality of variable distribution. Pearson's correlation analysis was used to determine the correlation between disease activity scores and US parameters with a normal distribution, and the Spearman's correlation analysis was used to determine the correlation between parameters with a non-normal distribution and ordinal variables. The Cohen's kappa (κ) statistic was used to test the agreement between clinical examination and US findings.

Results

Patient Characteristics

Of the patients included in the study, 91.9% (n = 57) were female and 8.1% (n = 5) were male. The mean age of the patients was 51.82 (11.71), and the mean disease duration was 117.94 (99.96) months. The clinical characteristics of the patients are presented in Table 1. Sixty patients were using at least one disease-modifying anti-rheumatic drug (DMARDs) either synthetic or biological or in some cases, both. Forty-three of these patients were using synthetic DMARDs, and 17 were using biological DMARDs whether in monotherapy or in combination.

Table 1: Demographic and clinical characteristics of the patients

	Mean (SD)
Age (years) (Min–Max)	51.82 (11.71) (24–77)
Disease duration (months) (Min–Max)	117.94 (99.96) (5–408)
ESR (mm/h)	22.13 (13.65)
CRP (mg/dl)	0.95 (1.00)
Swollen joint count (28 joints)	2.15 (2.73)
Tender joint count (28 joints)	5.65 (6.69)
HAQ	0.63 (0.52)
Morning stiffness (minutes)	49.68 (109.09)
Patients' global disease assessment score	4.48 (2.48)
Physicians' global disease assessment score	4.2 (2.12)
DAS28-ESR	4.04 (1.41)
DAS28-CRP	3.71 (1.24)
SDAI	17.29 (11.53)
CDAI	16.11 (11.30)
Mean US time (minutes)	24.8 (4.8)

SD: standard deviation, ESR: erythrocyte sedimentation rate, CRP: C-Reactive protein, HAQ: Health assessment questionnaire, DAS28: 28 joint disease activity score, SDAI: simplified disease activity index, CDAI: clinical disease activity index

Correlation between clinical, laboratory and ultrasonographic parameters

A significant correlation was found between the physician' global disease score and all US parameters except the number of joints with effusion and the effusion US score. No correlation between the global disease evaluation of the patient and any US parameters was found. No correlation was found with any US parameters between the patients' global disease scores and health assessment questionnaire (HAQ) as shown in Table 2.

No significant correlation between CRP and PD US findings and the number of joints with erosion was found, while weak correlations between CRP and other US parameters were detected. Significant correlations between ESR and all US parameters were found (Table 2).

No significant correlations between swollen joint count, joints with effusion count, and the effusion US score were noted, but a moderate correlation was found in terms of other parameters. Good correlation (r = 0.59, $P < 0.01$) between joints with erosion and swollen joints was found. A weak correlation between tender joint counts and the joints with erosion was found, but no significant correlation was found between other US parameters (Table 3).

Table 2: Correlation of clinical, laboratory, and ultrasonographic variables

	ESR	CRP	PtGDA	PhGDA	HAQ
SJC	0.27†	0.11	0.34*	0.59*	0.28†
TJC	0.26†	0.16	0.50*	0.68*	0.56*
US-SE	0.44*	0.46*	0.18	0.22	0.11
US-SP	0.38*	0.38*	0.23	0.34*	0.13
PDUS	0.30†	0.20	0.16	0.29†	0.20
PD-JC	0.26†	0.15	0.17	0.29†	0.24
SP-JC	0.27†	0.36*	0.21	0.31†	0.17
SE-JC	0.39*	0.44*	0.19	0.21	0.13
Synovitis	0.29†	0.27*	0.18	0.28†	0.19
US-Total	0.38*	0.35*	0.17	0.30†	0.16
Erosion-JC	0.26†	0.04	0.24	0.44*	0.16
PD ≥ 2	0.31†	0.32†	0.18	0.31†	0.18

* $P < 0.01$, † $P < 0.05$, US: ultrasound ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, PtGDA: Patient's global disease assessment, PhGDA: Physician's global disease assessment, HAQ: Health assessment questionnaire, SJC: Swollen joint count, TJC: Tender joint count, US-SE: Synovial effusion US score, US-SP: Synovial proliferation US score, PDUS: Power Doppler US score, PD-JC: Joint count with Power Doppler activity, SP-JC: Joint count with synovial proliferation, SE-JC: Joint count with synovial effusion, US-Total: Total US score, PD ≥ 2: Presence of at least 2nd degree PD signal

Table 3: Correlation of swollen and tender joint count, disease duration, morning stiffness, and ultrasonographic parameters

	SJC	TJC	Disease duration	Morning stiffness
US-SE	0.21	0.01	-0.02	0.11
US-SP	0.39*	0.06	0.11	0.15
PDUS	0.32†	0.04	0.11	0.13
PD-JC	0.30†	0.05	0.10	0.13
SP-JC	0.37*	0.04	0.03	0.12
SE-JC	0.19	0.06	-0.04	0.13
Synovitis	0.34*	0.01	0.08	0.96
US-Total	0.34*	0.05	0.06	0.13
Erosion-JC	0.59*	0.32†	0.45*	0.05
PD ≥ 2	0.29†	0.05	0.45*	0.21

*$P < 0.01$, † $P < 0.05$, SJC: Swollen joint count, TJC: Tender joint count, US-SE: Synovial effusion US score, US-SP: Synovial proliferation US score, PDUS: Power Doppler US score, PD-JC: Joint count with Power Doppler activity, SP-JC: Joint count with synovial proliferation, SE-JC: Joint count with synovial effusion, US-Total: Total US score, PD ≥ 2: Presence of at least 2nd degree PD signal

Correlations between clinical disease activity and US scores

No correlations between CDAI and US parameters, except the eroded joint count, were found. The eroded joint count correlated moderately with DAS28-ESR (r = 0.41; $P < 0.01$), DAS28-CRP (r = 0.42; $P < 0.01$), CDAI (r = 0.49; $P < 0.01$), and SDAI (r = 0.46; $P < 0.01$). The count of joints with synovial proliferation, synovitis, and PD signals, synovial proliferation US scores, and total US scores weakly correlated with DAS28-CRP, DAS28-ESR, and SDAI scores. No correlations between the synovial effusion US score, joint count with synovial effusion, and disease clinical activity scores were found (Table 4).

Table 4: Correlation of the disease activity scores and ultrasonographic parameters

	DAS28-CRP	DAS28-ESR	SDAI	CDAI
US-SE	0.21	0.25†	0.20	0.14
US-SP	0.28†	0.29†	0.28†	0.24
PDUS	0.23	0.23	0.25†	0.18
PD-JC	0.24	0.24	0.27†	0.20
SP-JC	0.28†	0.25†	0.26†	0.21
SE-JC	0.22	0.24	0.20	0.16
Synovitis	0.31†	0.30†	0.25†	0.19
US-Total	0.26†	0.27†	0.26†	0.20
Erosion-JC	0.42*	0.41*	0.46*	0.49*
PD≥2	0.24	0.23	0.26†	0.18

* $P < 0.01$, † $P < 0.05$, DAS28: 28 joint disease activity score, SDAI: simplified disease activity index, CDAI: clinical disease activity index

Correlations between clinical examination and US scores

In general, the correlation between clinical joint examination and US findings was weak (Table 5). A weak correlation between only swollen joints and B-mode (κ = 0.29) and PD-US when PD2 was used (κ = 0.31) was found, but no correlation between tender joints and US findings were noted (Table 5). When clinical examination of joints and the compatibility of the US were evaluated separately on a joint basis (Table 6), no correlation between clinical examination of the elbow with B-mode and PD-US was detected. While a

significant but weak correlation between B-mode and PD ≥ 2 tender and swollen joints at the wrist was found, no significant correlation between PD-US ≥ 1 was observed. A good/excellent significant correlation with swollen and both tender-swollen joints for PD ≥ 2 in the second MCP joint was found.

A weak correlation between joint tenderness in the second MCP joint and PD US score only was noted. A significant correlation between swollen joint and B-mode/PD-US was found, while a correlation between tender joint and US findings only for PD-US ≥ 1 in the third MCP joint was observed. The highest correlation between clinical and US findings was found in terms of the second MCP joint and knees, while the correlation of the wrist and third MCP joint was weak. In the elbow, no correlation between clinical and US findings was noted (Table 6).

Table 5: Agreement between clinical examination and ultrasonographic findings

		Swollen Joint	Tender Joint	Both Swollen and Tender Joint
Gray scale ≥ 1	%	77.9	64.2	75.3
	κ	0.295	0.069	0.146
PD ≥ 1	%	71.9	66.3	70.6
	κ	0.216	0.182	0.135
PD ≥ 2	%	84.8	72.7	86.1
	κ	0.313	0.167	0.246

κ: Kappa coefficient, %: percentage of concordance, Gray scale: Presence of at least grade 1 synovial effusion and/or synovial proliferation, PD ≥ 1: Presence of at least grade 1 and higher power Doppler signal, PD ≥ 2: Grade 2 and higher power Doppler signal

Table 6: Correlation of individual joints with the presence of gray scale and power Doppler (k values)

		Gray scale	PD ≥ 1	PD ≥ 2
Elbow	Tender	0.068	0.100	0.125
	Swollen	0.154	0.036	-0.016
	Swollen and tender	-	-	-
Wrist	Tender	0.270	0.051	0.223
	Swollen	0.270	0.049	0.208
	Swollen and tender	0.154	0.035	0.148
2nd MCP	Tender	0.106	0.241	0.247
	Swollen	0.375	0.415	0.568
	Swollen and tender	0.282	0.418	0.849
3rd MCP	Tender	0.028	0.219	0.012
	Swollen	0.227	0.243	0.349
	Swollen and tender	0.017	0.079	0.152
Knee	Tender	0.038	0.270	0.129
	Swollen	0.232	0.524	0.427
	Swollen and tender	0.101	0.337	0.307

MCP: Metacarpophalangeal joint, power Doppler (PD) ≥ 1: Presence of at least grade 1 and higher PD signal, PD ≥ 2: Grade 2 and higher PD signal

Discussion

In recent years, musculoskeletal US has frequently been used for early diagnosis of RA, assessment of disease activity and treatment response, and prediction of prognosis [20-22]. The goal of US use is to accurately determine disease activity and thus provide tight control of RA [23]. In the assessment of disease activity in RA, combined clinical activity indices, such as SDAI, CDAI, and DAS28, are traditionally used, and treatment decisions are based on these indices [5, 24, 25]. However, due to their subjective nature, these evaluation indices cannot directly measure inflammation at the primary site of pathology [26] and may be misleading about the actual disease activity [27]. This study was designed to assess the degree of correlation between disease activity indices, laboratory markers, clinical joint examination, and US findings in patients with RA, in addition to determining the degree of correlation between different joints. The number of joints with PD activity, total US scores, and synovial proliferation US scores all showed a weak correlation with clinical activity scores (SDAI and DAS28). No significant correlations with CDAI were found. In general, agreement between clinical joint examination and US findings was also weak.

Since the US can detect changes in the synovium directly, evaluation based on US is expected to be more accurate and more sensitive than clinical disease activity indices [28]. However, studies have shown different results about the degree of correlation between current disease activity indices and US findings [29, 30]. Compared with clinical examination, both grayscale and PD US have been found to be more sensitive for detecting synovitis [10, 16, 31, 32]. It has been suggested that the weak correlation between US findings and clinical joint examination can be explained by the high sensitivity of US [33]. Another theory may be that the correlation between clinical and US findings varies between different joints, and this finding may explain why a better correlation with clinical joint examination in studies conducted with a small number of joints exists [30].

One of the most important explanations for the discrepancy between the presence of a tender joint and US findings could be the presence of a PD signal on US even though no tender joint was found in the clinical evaluation. This difference could indicate the presence of ongoing subclinical joint inflammation, which is not detectable on clinical examination. Subclinical synovitis was identified in half of the patients who were assumed to be in remission based on clinical indices as reported in various studies [33, 34]. Subclinical synovitis is suggested to be the cause of persistent erosive damage in patients whose disease activity seems to be under control clinically [3, 35]. Despite low disease activity, persistent subclinical inflammation may explain the increasing erosion and destruction of joints in some RA patients [26].

The DAS28 score is one of the disease activity measurements used in RA and is frequently used in clinical practice for initiating and maintaining biological treatment. The DAS28 score multiplies the number of tender joints by a 2-times higher coefficient than the number of swollen joints. In the evaluation of disease activity, the number of clinically tender joints is assigned more weight than the number of swollen joints [3]. The fact that the number of tender joints rather than swollen joints have a greater effect on the DAS28 total score and the lack of correlation between tender joints and US findings may explain the discrepancy observed between disease activity scores and US findings. Fibromyalgia and degenerative pathologies that often accompany rheumatic diseases can cause widespread pain. Pain is frequently associated with RA by patients and may cause overestimated disease activity scores [36, 37].

The joints selected in studies with simplified joint scores are generally selected from those that correlate well with clinical joint examinations [12, 13, 38]. It has been shown that US using grayscale and PD-US is more sensitive than clinical joint examination for detecting synovitis and can reflect inflammation better than disease activity indices in patients with RA; thus a weak correlation exists between them [39, 40]. Naredo et al. [13] stated that the simplified 12-joint US evaluation is a valid, reliable, sensitive, and applicable method compared to the 44-joint US evaluation for the evaluation of joint inflammation in RA patients. It has been shown that a simplified 12-joint PD-US evaluation can identify 100% of patients with synovitis and 91% of patients with PD signals. In a

recent multicenter study, it was also reported that 22- and 6-joint US showed a strong correlation with each other, but a weak correlation with DAS28 scores was noted [41].

In this study, the existence of PD-US findings in joints with no clinical evidence of inflammation and no symptoms suggests subclinical synovitis, which has been linked to radiographic damage and clinical exacerbations. The absence of correlation between disease activity indexes, clinical joint examination, and US findings supports the view that clinical examination alone may not always be adequate for measuring disease and joint activities and that using US may lead to a significant improvement in the assessment. It has been shown that patients whose disease activity is monitored with US need less medication modification in the long-term, and their disease activity is more stable. [17]. A weak correlation between CRP and US parameters in our study may support the fact that acute phase reactants do not always accurately reflect subclinical inflammation. Additionally, if not combined with PD, the changes due to chronic joint degeneration in joints assessed using a grayscale alone may not yield adequate information regarding whether inflammation is present or not.

Limitations

This study has some limitations. The study was a single-center study. Other limitations include patients seen only at a single visit, changes in time were not observed, and the effect on the prediction of exacerbations could not be evaluated. Since US is a user-dependent subjective method, the operator's experience in US can be regarded as a limitation. The fact that the US operator may have noticed the symptoms of inflammation, such as joint swelling and warmth in addition to structural damage, such as deformities and synovial hypertrophy, may have generated a bias.

Conclusion

Accurate evaluation of joint inflammation via US may contribute to the opportunity for early diagnosis and lead to a better prognosis. It may be beneficial to add US to the existing RA disease activity indices and remission criteria to improve disease activity assessments and treatment outcomes. US may be a better tool than clinical evaluations to more accurately assess disease status, prevent exacerbations, and is applicable in the new definition of remission. Further studies with the simplified US methods are needed to determine the minimum number of joints to be evaluated and which joints should be selected for imaging to reduce examination time.

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Spontaneous enteroatmospheric fistula in a patient with COVID-19 disease

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Informed Consent
The authors stated that the written consent was obtained from the patient presented with images in the study.

Conflict of Interest
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Abstract

Coronavirus 2019 (COVID-19) disease patients present with upper respiratory symptoms; however, these patients may show gastrointestinal symptoms on arrival at the hospital. This finding requires an abdominal physical examination and imaging for 33% of patients. Enteroatmospheric fistulas (EAF) may form a connection between the external environment and the gastrointestinal tract and usually presents various difficulties in controlling the disease without surgical intervention. Its management requires a high level of clinical expertise to control and treat the fistula. In this case report, spontaneous EAF and its management are presented in a 65-year-old morbidly obese female patient who spontaneously had EAF during her hospitalization for COVID-19.

Keywords: COVID-19, Enteroatmospheric fistula, Open abdomen

Introduction

Coronavirus 2019 (COVID-19) disease was first reported in Wuhan in December 2019 and caused the pandemic that is ongoing at present. Although COVID-19 is pathogenic in all age groups, middle and older age groups who suffer with comorbidities have been reported to be at higher risk. The disease, which manifests itself with fever, cough, dyspnea, muscle aches, and weakness, can result in acute respiratory distress syndrome (ARDS), multiple organ failure, and death [1, 2].

This pandemic has also led to some drawbacks in inpatient management when elective surgeries have been cancelled, and a relative increase in emergency and oncologic surgery applications has been observed [2, 3]. Furthermore, an increase in general emergency surgery cases regarding more serious diagnoses, complications, and mortality has been noted [4].

Enteroatmospheric fistulas (EAF) are enteric fistulas that form a connection between the external environment and the gastrointestinal tract, thus forming an open abdomen. EAF management usually presents various difficulties. Many factors make it difficult for spontaneous closure of the fistula tract, so the primary target for the EAF management is to control the fistula in a chronic wound healing environment and operate at the right time for a definitive surgical repair. While various surgical approaches are used, the appropriate approach is specific to the patient's characteristics and is best managed by an experienced surgeon [5]. Our aim in this case report is to reveal the management process of EAF in a COVID 19 patient.

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Case presentation

This case report presents spontaneous EAF and management in a 65-year-old female patient during her hospitalization for the COVID-19 infection. Informed consent was obtained before the admission period. A 65-year-old morbidly obese female patient who had hypertension and type 2 diabetes mellitus (DM) with COVID-19 infection presented in our department after spontaneous intestinal drainage from her anterior abdominal midline incision scar. She was hospitalised 18 days ago by the internal medicine clinic for a COVID-19 infection that manifested as bilateral pulmonary infiltration. Physical examination revealed an enteroatmospheric fistula orifice approximately 2 cm below the umbilicus and 1 cm left of the midline (Figure 1). Skin rashes were remarkable due to chronic irritation by intestinal drainage with biliary content. She was immobile due to her morbid obesity. Her history revealed that she had an open cholecystectomy and incisional hernia repair by an upper midline incision. A recurrent incisional hernia was found on physical examination. While contrast-enhanced abdominal computed tomography (CT) had confirmed the fistula tract (Figure 2), the thorax CT findings were compatible with typical pattern of COVID-19 pneumonia (Figure 3). She tested positive for COVID-19 based on polymerase chain reaction (PCR) and laboratory values with a D-dimer level of 2800 ng/mL, C-reactive protein (CRP) 30 mg/L, and creatinine level of 1.22 mg/dl. Our general surgery clinic took over her clinical follow-up. She had an advanced COVID-19 infection, so our primary therapy aimed to control the fistula during COVID-19 therapy. First, an abdominal vacuum-assisted closure (VAC) device was applied, but it was unsuccessful due to inflammation in the surrounding tissues. Therefore, surgery was planned under COVID precautions. The patient was operated on under sedation. Exploration revealed that the mesh belonging to the old operation and the herniated bowel loops under it were highly adherent and fistulised from this area. Further dissection did not help the surgeons enter the unhealthy abdominal cavity or repair the incisional hernia. The fistulised bowel loop was separated from the hernia sac and surrounding tissues and a temporary stoma through the skin was formed by suturing the lateral borders (Figure 4). Post-operatively, VAC was applied around the temporary stoma to cause fistula maturation. Broad-spectrum antibiotics were started.

Figure 1: Spontaneous fistula of the Coronavirus 2019 (COVID 19) patient revealed by physical examination

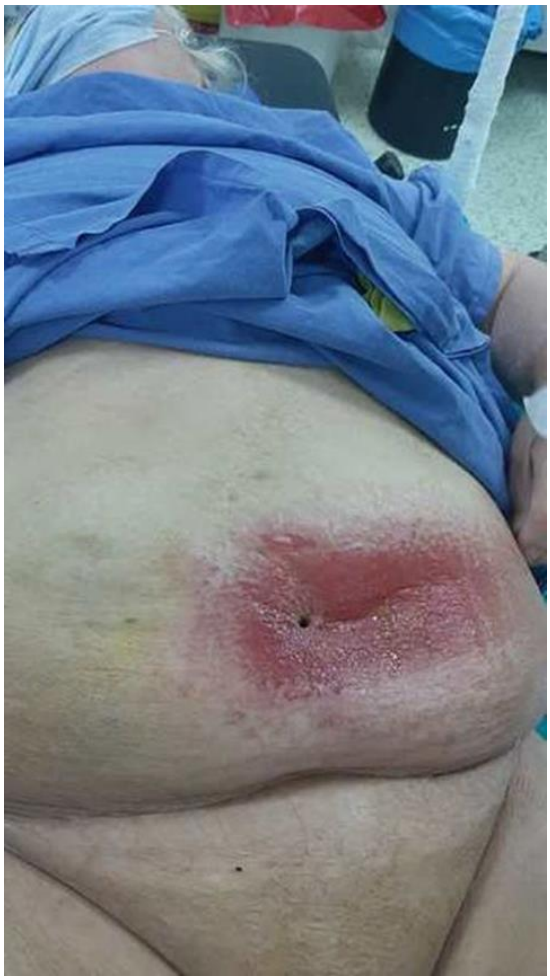


Figure 2: Fistula tract on abdominal computed tomography (CT)

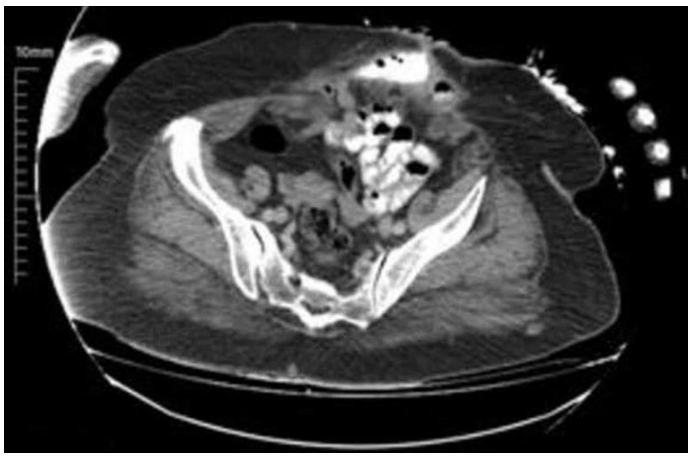


Figure 3: Pulmonary infiltrations due to COVID 19 disease

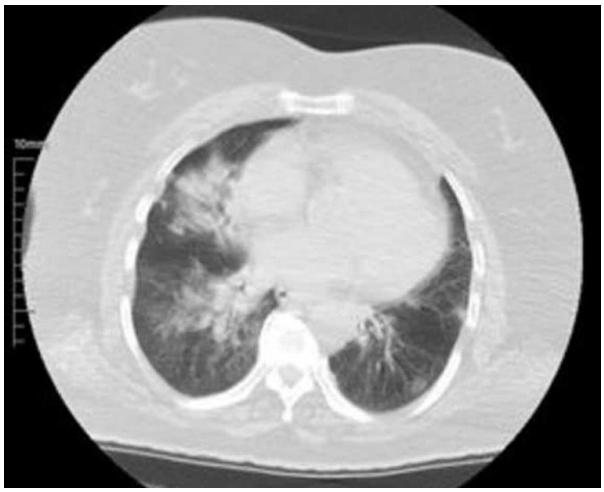
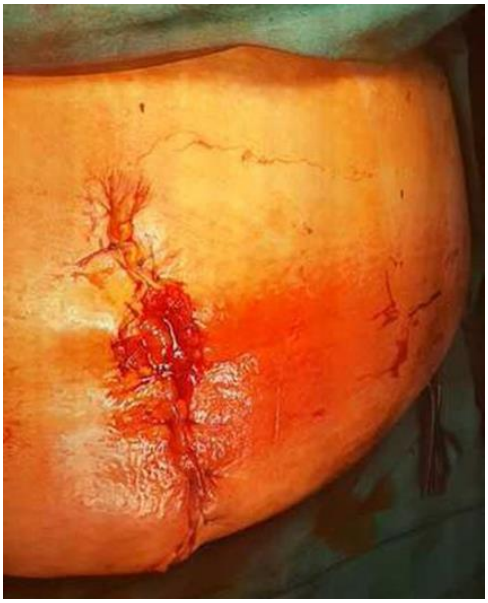
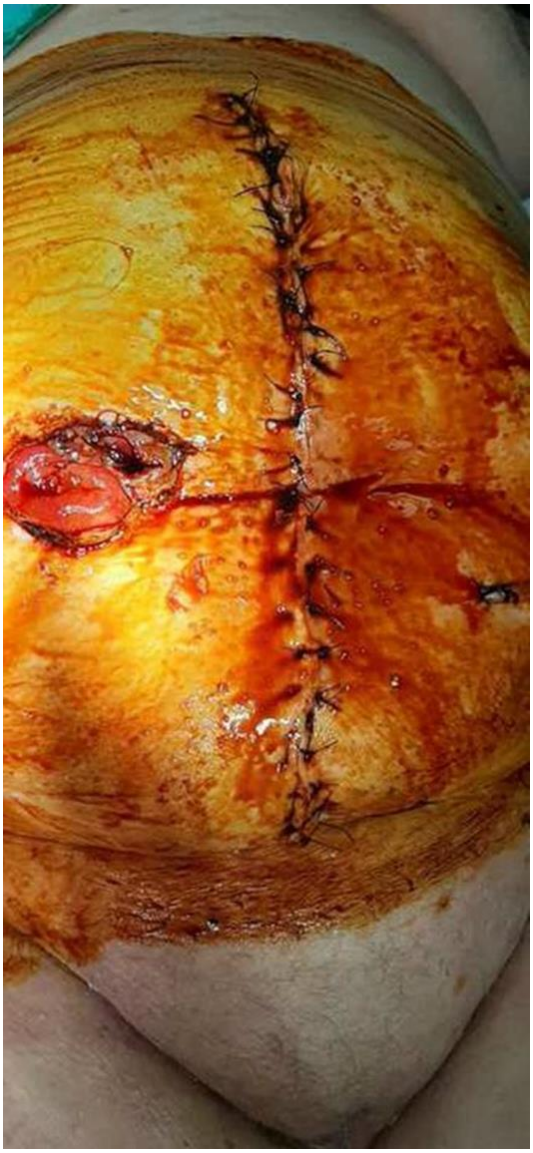


Figure 4: Fistula tract was matured as temporary stoma after first surgery



Antiviral and supportive treatments were administered during the post-operative period according to the current COVID-19 protocols. The control PCR test was negative. Her pulmonary function improved, which was demonstrated on a follow-up thorax CT. In the intensive care unit (ICU) follow-up, VAC application was found to be ineffective after one week of therapy, so a definitive approach was decided for the patient who was more suitable for definitive surgery. Surgical exploration revealed that the patient had dense adhesions in the entire abdominal cavity due to previous hernia repair with an onlay mesh placement. The fistulised area of 50 cm unhealthy bowel segment that was 200 cm from the Treitz ligament was resected. The proximal and distal small bowel segments were pulled through the skin in the form of a double-barrel ileostomy (Figure 5). The post-operative follow-up showed that the ileostomy was not effective due to stenosis, so the patient's ostomy was revised under sedative anaesthesia. After the stoma revision, her clinical condition improved, and the inflammation in the skin and the septic condition had regressed. After extubation, the patient was transferred to our service. On the second day of the service follow-up, the patient's state of consciousness deteriorated. The patient was intubated electively and taken back to intensive care. The patient died due to a massive pulmonary embolism as revealed by a contrast-enhanced thorax CT.

Figure 5: Double-barrel stoma after definitive surgery



Discussion

Several studies in the literature on enteroatmospheric fistula treatment are available. This case report is the first describing a spontaneous enteroatmospheric fistula and its management in a patient who had complications due to a COVID-19 infection. Due to the current pandemic processes, limited information about the choices and timing of treatment to be applied to this patient group and the difficulties that may be encountered in the management of the perioperative process is available [1–3].

Hospital administrations face increasing difficulties in managing critical resources during the pandemic, such as wards, intensive care units, ventilators, and protective equipment [1–3]. Surgeons must consider local COVID-19 resources. Surgeons must strictly follow two basic procedures: (1) safety and (2) precautions. The first question the surgeon should answer when confronted with a patient with COVID-19 disease is: "Is the patient suitable for non-operative treatment, or can surgical treatment be postponed?" Patient triage is crucial in determining the non-operative or operative approach. If the patient's clinic is not suitable for non-operative follow-up, the golden rule is to work with a minimum number of well-protected healthcare personnel. Close clinical and radiological follow-up at 12 to 24-h

intervals is required in patients selected for a non-operative treatment approach until their condition stabilizes. Surgery is inevitable if the patient's symptoms, such as abdominal pain, fever, and shock, persist or become aggravated [1–3].

Among the primary factors that can lead to the development of EAF are anastomotic leakage, serosal injuries, contact with surgical materials used in abdominal closure of dehydrated bowel loops, wound site infections, organ injuries, traumas and ischemia. After the enteroatmospheric fistula is formed, the primary approach in treating this complicated condition is to control the fistula tract. Considering the etiological factor of the fistula and the co-morbid conditions present in the patient, the use of medical and advanced surgical methods should primarily be involved in managing the disease [5, 6].

Bhayane et al. [7] stated that 34% of patients hospitalized for COVID-19 showed gastrointestinal symptoms on arrival, and 33% underwent abdominal imaging. In this study, three of four patients who had signs of bowel ischemia on a CT and underwent a laparotomy, gangrenous changes in the intestines were observed. Necrotic mucosal changes were detected based on pathological examinations. In the other patient, patchy yellow discoloration was detected on the antimesenteric side of the intestines. It has been stated that the potential causes leading to a clinical condition in these patients infected with COVID-19 may be the direct effects of viral infection on the small vessel thrombosis or mesenteric ischemia without occlusion. Angiotensin converting enzyme (ACE) 2 surface expression is most abundant in the lung alveolar epithelium, enterocytes of the small intestine, and vascular endothelium, suggesting that the small bowel and vasculature may be susceptible to COVID-19 infection.

In the case report prepared by Costanzi et al. [8] concerning a patient who developed a colo-vaginal fistula on the 31st post-operative day after a low anterior resection as performed, the authors stated that late bowel ischemia might develop in surgical patients due to a small vessel thrombosis associated with COVID-19. In our patient, it is thought that the mesh used in the previous operation and this ischemic process may be the primary factors in her EAF development [9].

Regulation of nutrition in the general medical management of the disease is essential for clinical progression. The possibility of fluid and intestinal content losses, peritonitis, and body stress response can put patients into a hypercatabolic process. First, a patient’s hemodynamic stability should be ensured, electrolyte imbalance should be corrected, and acid-base balance should be provided. Wide spectrum antibiotherapy should be used for the septic process. Total parenteral nutrition (TPN) should be started as soon as possible. The anatomy of EAF, continuous intestinal surface, and length suitable for enteral nutrition should be carefully determined to establish a good nutrition plan. Although the advantages of enteral feeding over TPN are known, it should be considered that it will increase the fistula flow rate [5, 6].

The surgical approach contains difficulties, such as the fistula’s sensitivity and surrounding tissues, severe dehydration, a septic process that develops due to intraperitoneal leaks, and intra-abdominal adhesions that restrict intra-operative manipulation. When EAF develops, hidden fistulas, distal obstructions, foreign bodies, neoplasms, inflammatory bowel diseases, and distal obstructions may lead to the septic process and spontaneously prevent the fistula's closure. Thus, optimal medical and surgical treatment is essential [5, 6, 10–12].

In our case, the patient died although early nutritional therapy had commenced, and infectious precautions were taken for local control of the fistula. Her death was possibly related to COVID-19 infection and its deleterious effect on the patient’s clinical condition and her comorbidities. VAC therapy was preferred in literature as in our case [9]. Unfortunately, the patient’s clinical condition was not conducive to the continuation of the treatment in this way. Surgical interventions were performed to control the EAF, which were successful but may have contributed to the pro-inflammatory environment that led to the immobilized patient's septic condition and pulmonary embolism.

Conclusion

COVID-19 might present with gastrointestinal symptoms or manifest with complications during the peri-operative period. Surgeons should be aware of the possible deleterious effects of COVID-19 during patient management. During management of the clinical situation of the patient, optimal timing of surgical intervention may be required to avoid the additional burden of COVID-19 disease.

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Oromandibular dystonia seen during pramipexole treatment: A rare case

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Informed Consent
The authors stated that the written consent was obtained from the patient presented with images in the study.

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

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Abstract

Dystonia is an abnormal, often repetitive, bending/twisting behavioral disorder characterized by continuous or intermittent muscle contraction. Oromandibular dystonia (OMD) is a type of dystonia involving chewing, mouth circumference, tongue, and platysma muscles. OMD is divided into different clinical types, including jaw opening OMD, jaw closing OMD, and mixed type OMD. OMD may either be primary or secondary to other diseases. The average patient age is between 50 and 60 years, and several studies have shown that it is more common among women. Dystonia may occur either as idiopathic (primary) or resulting from neurodegenerative diseases and other secondary dystonia. OMD can cause difficulty in speaking, chewing, and swallowing and produce pain during these movements. Therefore, OMD can lead to deterioration in an individual's daily life and social relationships. Although dopaminergic drugs can be used in the treatment of dystonia, the aim of the study was to report that these drugs may also be a factor in further development of dystonia and to attract the attention of clinicians to this anomaly.

Keywords: Oromandibular dystonia, Pramipexole, Dopamine agonist, Restless leg syndrome

Introduction

Dystonia is a continuous or intermittent muscular contraction-induced movement disorder that can often involve repetitive motions and involuntary bending/twisting. Dystonic movements are characterized by bending or sometimes tremors. Dystonic movements almost always become intensified during voluntary acts. Expansion of dystonic posture to close and even remote muscles during a volitional act is defined as 'overflow' [1]. Dystonia is divided into two categories depending on its etiology and clinical features, such as age of onset, body distribution, time-related features, and co-occurrence with other movement disorders or neurological or systemic symptoms [2]. A diagnosis of dystonia is based on its clinical features.

Oromandibular dystonia (OMD) is a type of dystonia involving masticatory, circumoral, lingual, and platysma muscles. OMD has different clinical sub-types, including jaw-opening OMD, jaw-closing OMD, and mixed type OMD. OMD can be a primary disorder or secondary to another disease. Patients are classified as having focal, segmental, multifocal, and generalized dystonia depending on the bodily distribution of dystonia. While OMD may appear focally, it is mostly a part of segmental and generalized dystonia [3]. The average age of incidence occurs between 50 and 60 years of age. Various studies have reported that OMD occurs more in females [3, 4]. OMD may lead to difficulty in speaking, chewing, and/or swallowing and cause pain during these activities that lead to impairment of daily life and social relationships [5].

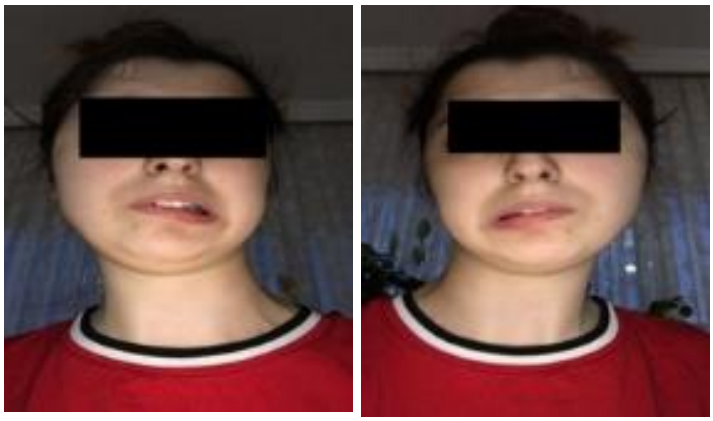
The aim of this article was to report that while dopaminergic drugs have a role in dystonia treatment, oromandibular dystonia may appear as an adverse acute reaction during pramipexole treatment and to bring this anomaly to the attention of clinicians.

Case presentation

A 25-year-old single female high-school graduate presented to the Neurology Polyclinic with complaints of an abnormal and displeasing sensation that had been occurring for a couple of years on her feet, especially during rest periods and at night. These complaints were forcing her to move her legs uncontrollably as her complaints were relieved when she stood up and wandered around. The patient had no other characteristics in her medical history. The patient received pramipexole 0.250 mg 1x1 tb treatment. The patient presented to our hospital's emergency department two days after the start of treatment as she had deviation to the right and left in perioral muscles and lips (Figures 1A and 1B). The patient was administered one ampoule (5 mg) of intramuscular biperidene treatment in the emergency department. The patient's complaints were relieved after administration of the biperiden treatment. The patient's neurological examination performed in the emergency department was completely normal except for the finding of dystonia in the perioral muscles. No pathology was found based on patient's routine blood tests, brain magnetic resonance imaging, electroencephalography, and electromyography (MRI, EEG and EMG, respectively) examinations performed in the neurology clinic for determining the etiology of her dystonia. The patient was discharged with recommendations.

Figure 1A: Oromandibular dystonia (OMD) in the lips and perioral muscles in the form of left shift

Figure 1B: OMD in the lips and perioral muscles in the form of right shift



Discussion

Dystonia is a movement disorder characterized by repetitive, bending, twitching, painful, and prolonged muscle contractions in the affected body part. OMD is a focal form of dystonia where the facial, lingual and jaw muscles are affected. While dystonia may be idiopathic (primary), it may also be induced by neurodegenerative diseases and other secondary issues associated with dystonia.

In the literature, no case reports concerning the occurrence of pramipexole-induced oromandibular dystonia can be found. Only a few case reports on pramipexole-induced limb dystonia and antecollis in Parkinson's disease are available. In one case, extremity dystonia with sub-acute onset following pramipexole treatment was reported in a Parkinson's disease patient receiving levodopa/carpidopa treatment. In a previous case report on pramipexole-induced extremity dystonia in Parkinson's disease, the authors presumed that although pramipexole showed a rather low affinity for serotonergic receptors, dystonia in the extremities occurred resulting from a potentially reactive fibrosis appearing at the serotonergic 5 HT2A and 5HT2B receptors [6]. However, the further increase in dystonia severity following cessation of pramipexole treatment suggests that the source of dystonia cannot be explained by a simple fibrotic complication. Moreover, abnormal activation of D1 receptors is a mechanism that could play a critical role in the occurrence of dystonia [7]. Activation of D3 receptors in the striatum has synergistic effects on D1 receptor-mediated transmission. Pramipexole shows a more evident affinity primarily for D3 receptors [8]. Antecollis is a form of dystonia that was first been shown in multi-system atrophy (MSA) patients, and it is a helpful indicator used in the diagnosis of MSA disease [9]. Antecollis is relatively rare in Parkinson's disease, and its pathophysiology is uncertain. However, several central and peripheral mechanisms have been suggested to be responsible for causing this condition [10]. In literature, antecollis cases associated with pramipexole treatment in Parkinson's disease have been reported [11]. In another case report, a female patient receiving trihexiphenidyl, pramipexole, and resagiline triple treatment was reported to have jaw dystonia characterized by lateral deviation to the right and left that was seen after the addition of levodopa/carpidopa to her current treatment. This jaw dystonia was reported to have occurred at the time when levodopa/carbidopa treatment reached its peak level in the blood. It was observed that while jaw dystonia disappeared with the gradual reduction in levodopa/carbidopa treatment, the on–off phenomenon appeared in the patient. Controlled release forms of Levodopa/carbidopa were found to be ineffective in the treatment of dystonia [12]. In the literature, two case reports concerning oromandibular dystonia associated with levodopa/carbidopa treatment are available. One of these patients was treated for Parkinson's disease, and the other was treated for progressive supra-nuclear palsy [13, 14]. Levodopa-induced dyskinesia is mainly and typically characterized in the choreiform and is noticed seen when Levodopa reaches its peak dose level. Dyskinesia may appear in the form of dyskinesia less frequently and is presumed to be in the form of dystonia in biphasic dyskinesia with a wearing off pattern. Dystonia, which Levodopa can induce as a peak dose phenomenon, is quite rare [15].

Conclusion

Clinicians should consider dopamine agonists as a factor leading to the development of dystonia because this condition can be reversed when recognized early. In our case, it was not possible to explain how pramipexole caused acute dystonia. Yet, it is considered that OMD could appear due to abnormal stimulation in D1 receptors resulting from pramipexole stimulation of D3 receptors. Moreover, the genetic makeup of the patient is assumed to be a factor that is influential in the development of pramipexole-induced acute dystonia. Further studies could yield a better understanding of the pathophysiology of the development of pramipexole-induced OMD.

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Intradural migration of fusion cage in an isthmic listhesis patient treated with transforaminal lumbar interbody fusion (TLIF): A case report

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Abstract

Lumbar listhesis, is defined as a disorder that causes a vertebral body to slip over the one below it. Several surgical decompression and augmented fusion techniques are available for treatment. Transforaminal lumbar interbody fusion (TLIF) is a commonly used surgical technique for degenerative lumbar spondylolisthesis in cases in which conservative care fails to achieve satisfactory spinal fusion. Although TLIF is widely accepted because it is easy to perform and is very safe, cage migration is an important complication, and posterior migration is a serious one. Cage migration can be classified as posterior, anterior, or sagittal forms according to migration direction. An increasing number of the surgeons have encountered cage migration; however, consensus on its cause is lacking. In this report, a case of intradural cage migration with left leg pain is presented, and this complication is discussed in light of related studies.

Keywords: Listhesis, Cage migration, Risk factors, Transforaminal lumbar interbody fusion, TLIF, Complication

Introduction

Listhesis is defined as a disorder in which one vertebral body slips over the one below it [1]. Lumbar listhesis often results in both low back and leg pain related to spinal stenosis [2]. Indications for its surgical treatment include persistent or recurrent back pain and/or leg pain, progressive neurological deficits, and neurogenic claudication [3]. Several surgical techniques for decompression and augmented fusion can be performed, each of which has its own merits and limitations [4]. Both Posterior lumbar and transforaminal lumbar interbody fusion (TLIF) are two commonly used surgical techniques for treating degenerative lumbar spondylolisthesis in cases in which conservative care fails to achieve spinal fusion [5]. TLIF is widely accepted because it is easy to perform and very safe**.** However, cage migration is an important complication as posterior migration, in particular, is quite serious since it can cause compression of the nerve root or dura mater and intensify a patient's neurological symptoms. Cage migration can be classified as posterior, anterior, or sagittal according to its direction [6]. An increasing number of surgeons have encountered cage migration; however, no consensus regarding this complication exists. In this study, a case of an intradural migrated cage with left leg pain is presented, and this complication in light of the literature is discussed.

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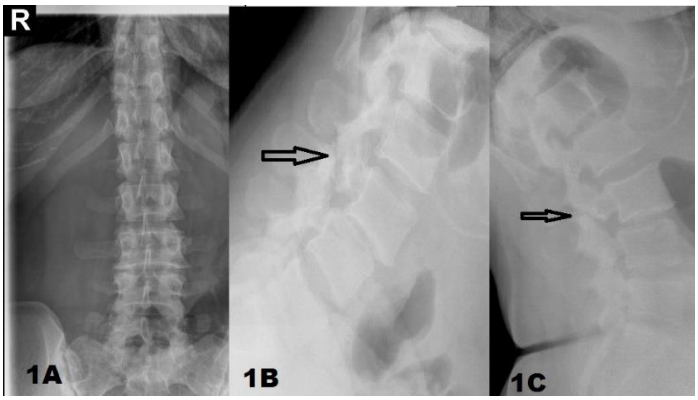
Case presentation

A 36-year-old female patient had a 5-year history of bilateral leg and back pain and neurogenic claudication. Medical and physical treatments were unsuccessfully performed for five years. She presented to our neurosurgical polyclinic as an outpatient and underwent a neurological examination, standing flexion and extension X-rays (Figure 1A–C), and lumbar magnetic resonance imaging. According to the Meyerding classification, Grade 1 isthmic listhesis, bilateral foraminal stenosis, and subligamentous disc herniation were observed between the third and fourth lumbar levels. The patient was given the diagnosis, and surgery was recommended after which an informed consent was obtained. During surgery, a conventional midline incision was made, and a total laminectomy, bilateral inferior facetectomy, and bilateral discectomy were then performed. Before the TLIF was performed, polyaxial screw fixation was performed at the third and fourth bilateral lumbar pedicles after which the disc space was expanded due to pedicle screw distraction. Thereafter, bilateral discectomy was repeated, and a 6-mm TLIF filled with patient bone was applied in the disc space. After TLIF application, pedicle screw compression was performed. Four days later, the patient was discharged with no complaints.

Figure 1: Pre-operative anterior-posterior X-ray view (1A), pre-operative flexion (1B) and extension (1C) X-ray views show Grade 1 isthmic listhesis and foraminal stenosis



One month later, the patient returned for a follow-up with no complaints. Three months later, a lumbar X-ray (Figure 2A, B) revealed slight posterior TLIF migration; however, it was decided to continue following up. At six months post-surgery, she returned to the hospital complaining of back pain, and another lumbar X-ray (Figure 3A, B) revealed further posterior TLIF migration. A second surgery was recommended, but the patient declined in favor of continuing to follow only. Nine months later (at 16 months post-surgery), the patient returned to the hospital complaining of left leg pain. A lumbar X-ray (Figure 4A, B) and computed tomography (CT) revealed that the TLIF migration had progressed further (Figure 5A, B). Revision surgery was recommended for which the patient provided informed consent. It was initially thought that the TLIF was in the left foramina, butit could not be seen in that location. Thereafter, the dissection was expanded toward the ventral lumbar dura, and it was seen that the TLIF had migrated into the posterior lumbar dura (Figure 6). An attempt was made to withdraw the TLIF, but resistance was encountered in its anterior portion. After pedicle screw distraction, and the TLIF was withdrawn easily. The ventral and posterior dura (Figure 7) were then closed. The screw fixation system was re-established, a closed suction drain system was placed, and the anatomical layers were closed. On the first post-operative day, she had no complaints and walked without assistance. On the fifth post-operative day, the patient was discharged with no complaints or complications.

Figure 2: Three-month follow up anterior-posterior (2A) and lateral (2B) X-ray views showed slight posterior transforaminal lumbar interbody fusion (TLIF) migration.

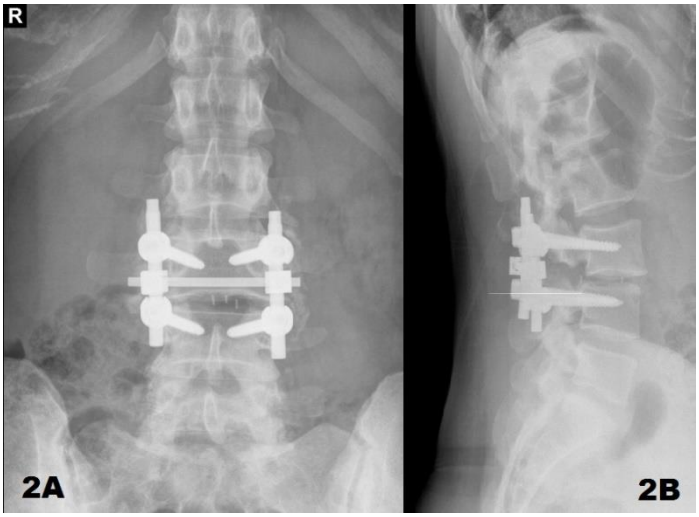


Figure 3: Six-month follow up anterior-posterior (3A) and lateral (3B) X-ray views showed further posterior TLIF migration.

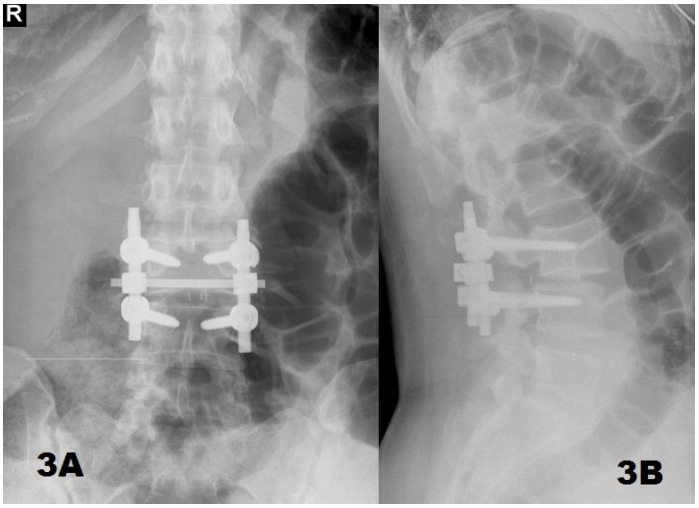


Figure 4: Sixteen-month follow up anterior-posterior (4A) and lateral (4B) X-ray views showed progressed further TLIF migration

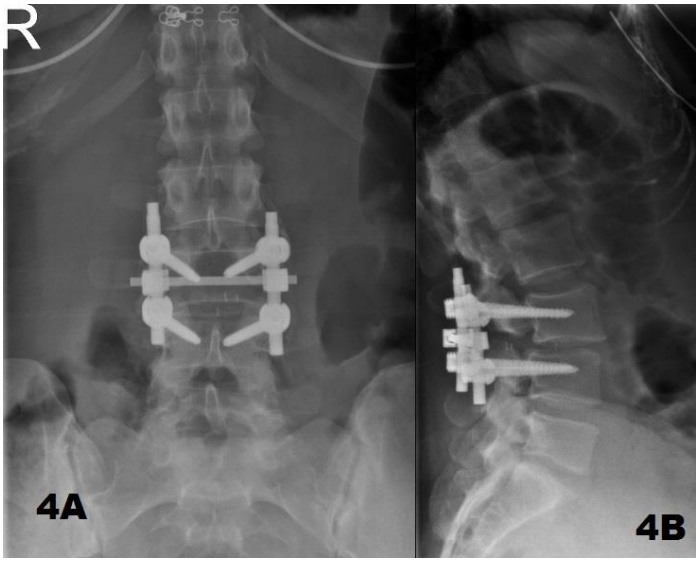


Figure 5: Sixteen-month follow-up saggital (5A) and coronal (5B) computed tomography (CT) sections showed progressed further TLIF migration and bilateral L3 and L4 screw loosening.

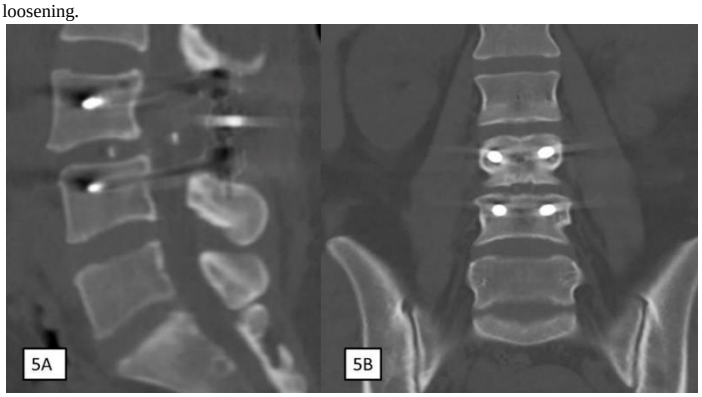


Figure 6: Intradural cage migration

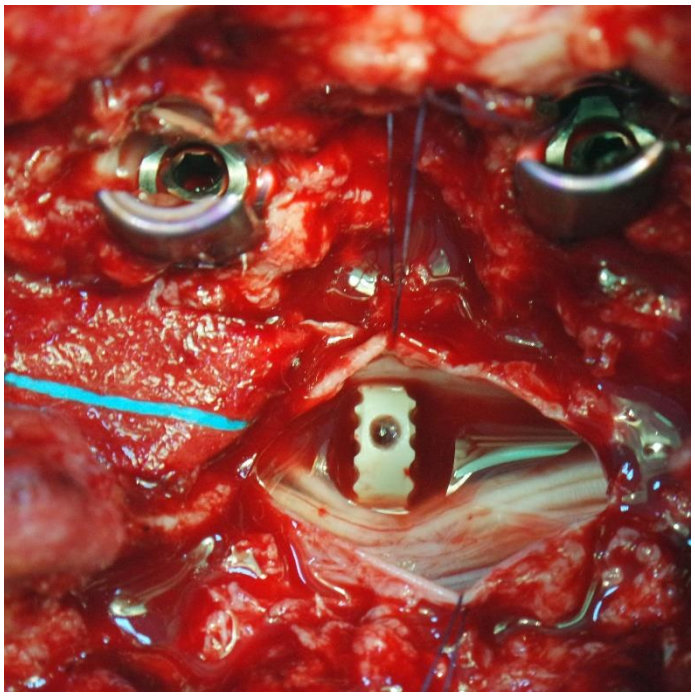
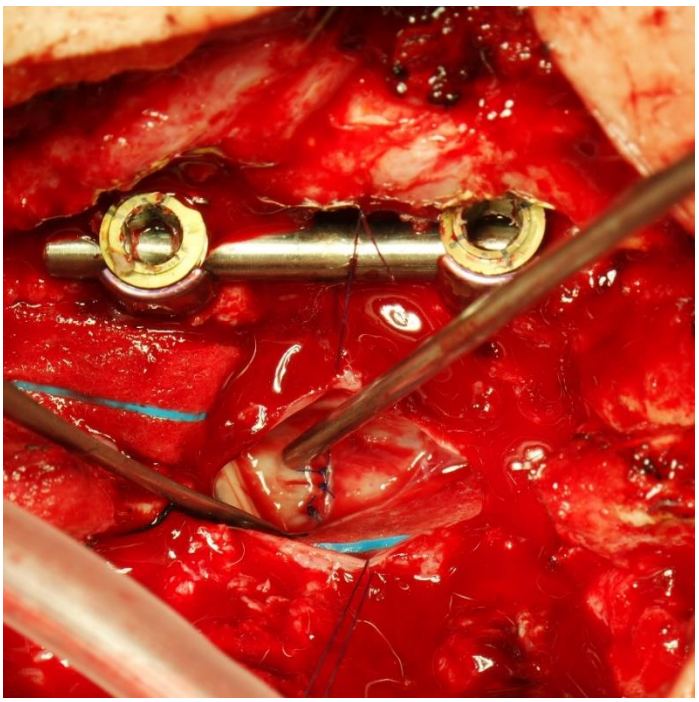


Figure 7: Closed ventral dura after withdrawing the TLIF



Discussion

The popularity of TLIF has increased over the past decade because fusion rates after TLIF application and bilateral pedicle screw instrumentation are reportedly 90%–100% [7, 8]. Different surgical approaches have been developed for TLIF placement. One such approach is an open technique that has been performed thanks to posterior decompression and simultaneous interbody fusion, while another involves minimally invasive TLIF placement. Both techniques have advantages and disadvantages. TLIF placement using the traditional method requires a posterior midline approach in addition to retraction of the thecal sac and nerve roots. Therefore, all complications encountered during TLIF placement are related to this approach. In the literature, many different studies have reported the possible complications of the open surgical technique [5, 7, 9]. TLIF cage migration is a post-surgical complication that may occur in the posterior, lateral, or anterior direction [6]. Although cage migration may be asymptomatic in some cases, posterior migration may be the most important because its symptoms may appear soon after surgery.

Many possible factors related to TLIF migration, such as excessive endplate abrasion, TLIF size and type, endplate type (concave–concave or linear–linear), the presence of the scoliotic curvature, greater posterior disc height, and TLIF performed without or unilateral instrumentation have been identified [6, 10, 11]. In the light of our case and those in the related literature, many reasons for TLIF migration can be suggested. However, some reasons related to our case, such as excessive endplate abrasion, greater posterior disc height, linear–linear endplate type, scoliotic curvature, and TLIF performed without instrumentation, can be separated from the others. Our patient had the necessary endplate abrasion, a concave–concave endplate, no scoliotic curvature, and TLIF was performed with instrumentation. Therefore, cage type, size, and surgical technique may have been factors in our case. In the literature, rectangular-shaped and small cages have been reported to migrate more frequently than kidney-shaped and large cages [6]. In our case, although a kidney shaped TLIF was used, another important factor in the emergence of this complication might be the size of the TLIF. At first, a 6 mm TLIF was freely tried before expanding the distance with the screw system; however, it did not stretch the distance. Therefore, it was thought that TLIF above these dimensions would cause endplate abrasion. For this reason, it was felt that a 6 mm TLIF would be sufficient. To suggest a self-criticism in this situation, although the entrance of TLIF was narrower than 6 mm, the concave–concave surface of the intervertebral disc could also have allowed the application of larger sizes of TLIF than the actual applied one since the middle part of the intervertebral disc was higher.

In this surgical technique title, bilateral or unilateral inferior facetectomy, inadequate discectomy or failure load, and flexibility may be factors for the failure. In the literature, spinal biomechanical studies have shown that the interface between the endplate and the fusion cage is subject to extreme pressure [12, 13]. Therefore, excessive pressure, such as that exerted by pedicle screw compression, may be a factor contributing to endplate fracture or fragility. In this way, intervertebral disc space may be expanded post-operatively, which can facilitate

TLIF migration. Another factor is screw malposition, which can cause inadequate loading and lead to an increase in the risk of TLIF migration. Our case demonstrated neither excessive loading nor screw malposition and inadequate discectomy. The inferior facetectomy may have been a factor for TLIF migration in our case. In the literature, Aoki et al. reported that a unilateral facetectomy could cause TLIF migration because the pedicle could have been mechanically injured prior to pedicle screw fixation during the TLIF procedure. This resection could have caused mechanical injury to the pedicle on the same side [10]. However, a bilateral inferior facetectomy was performed in our case because of the patient's reported bilateral radicular pain due to midline disc herniation and facet instability. This state can be a secondary factor contributing to mechanical injury of the pedicles. Because of the technical implementation of TLIF, the disk space needed to be widened and then compressed. These distraction and compression movements may have caused enlargement of the screw-inserted pedicle of the vertebral segment whose cortex integrity was disrupted by inferior facetectomy. In our case, the finding that supports our view is loosening appearances around the screws in the bilateral L3 pedicles occurred as viewed on the coronal sections of the CT scan. This screw loosening may have decreased the compression force on TLIF, facilitating pseudo-union in the disc space and then removal of the TLIF.

Conclusion

Intradural TLIF migration can occur, and surgeons must remain alert to its possibility. The posterior dural approach can be used to withdraw TLIF and reduce the risk of caudal fiber injury. In addition, many reasons for TLIF migration exist. Bilateral inferior facetectomy can be a factor, but how it affects TLIF migration must be investigated in future mechanical studies.

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Papillary thyroid cancer in a child with hemophilia A

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The authors stated that the written consent was obtained from the parents of the patient presented with images in the study.

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Abstract

Hemophilia A is a hereditary hemorrhagic disorder associated with bleeding episodes and characterized by deficiency or dysfunction of coagulation protein factor VIII. Cancer incidence was found to increase in hemophilic patients. A case of a 6-year old boy with papillary thyroid cancer and hemophilia who underwent a successful total thyroidectomy and bilateral modified radical lymph node dissection with appropriate peri-operative management consisting of Factor VIII replacement is presented.

Keywords: Hemophilia A, Child, Papillary thyroid cancer

Introduction

Hemophilia A is a genetic hemorrhagic illness marked by a lack of or dysfunction of coagulation protein factor VIII, which is linked to bleeding episodes. Hemophiliacs may develop a variety of medical and surgical issues (such as cardiovascular diseases, malignancies, and renal disease) as they age, and the consequences of aging become more apparent. Cancer incidence was found to increase in hemophilic patients. A literature search for malignancies in patients with hemophilia revealed that hepatocellular carcinoma, lymphoma, urogenital cancers, leukemia, gastrointestinal cancers, and respiratory tract cancers are the most common malignancies [1–3]. A case of a 6- year old boy with papillary thyroid cancer and hemophilia who underwent a successful total thyroidectomy and bilateral modified radical lymph node dissection with appropriate peri-operative management consisting of Factor VIII replacement is presented.

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Case presentation

In March 2016, a 6-year-old hemophilia patient undergoing prophylaxis treatment and with a history of past intracranial bleeding presented to the Pediatric Hematology Clinic with neck swelling. Neck ultrasound imaging showed an enlargement of the thyroid gland, diffuse punctate calcifications, heterogeneous nodules, and right cervical lymphadenopathy. Thyroglobulin levels were significantly higher (410 ng/ml), and lymph node excisional biopsy was performed on the patient. Papillary thyroid cancer and lymph node metastasis were identified based on the biopsy. He underwent a successful total thyroidectomy and bilateral modified radical lymph node dissection with appropriate peri-operative management consisting of Factor VIII replacement (Figure 1). Pathological examination of the tumor showed that the type and subtype of thyroid cancer was classic type papillary thyroid cancer, multisegmental and multifocal. The tumor was found to have spread beyond the thyroid via thyroid capsule invasion, lymphatic invasion, and blood vessel invasion (Figure 2). After surgery, the patient was admitted to the nuclear medicine department for iodine treatment. Oral radioactive iodine treatment for thyroid ablation was then administered. Levothyroxine sodium treatment was started after radioactive treatment, and it was decided to discharge the patient from the service. The patient is still seen on an outpatient basis to undergo routine thyroid monitoring, including thyroid function tests, anti-thyroglobulin antibody test, whole body iodine screening, and other hematological blood tests in addition to arranging his treatment. Informed consent was obtained from the patient's family for scientific presentation of the case.

Figure 1: Six-year-old haemophilia patient. Total thyroidectomy and bilateral modified radical lymph node dissection

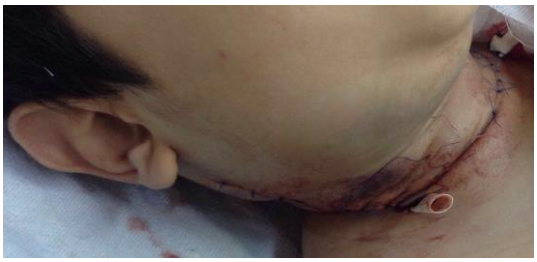
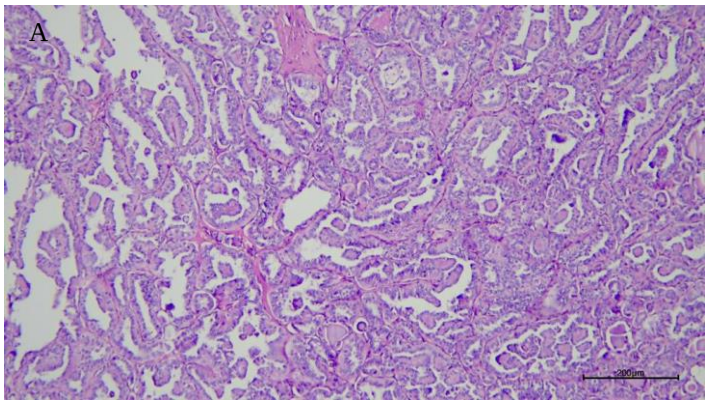
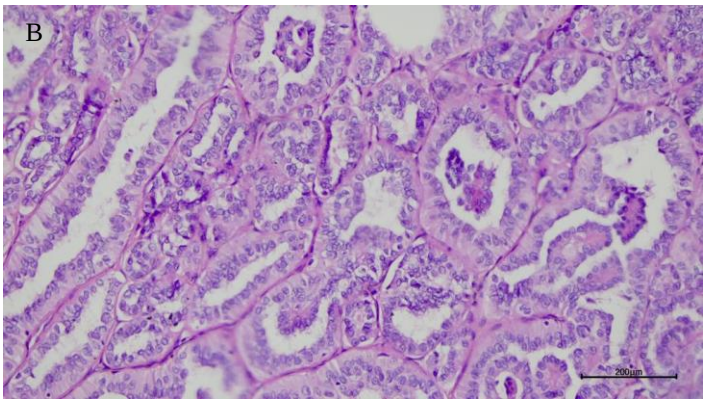


Figure 2: Classic type papiller thyroid cancer, multisegmental and multifocal. Tumor spread beyond the thyroid via thyroid capsule invasion, lymphatic invasion, and blood vessel invasion. A: x100, B: x200





Discussion

Life expectancies of patients with hemophilia have dramatically improved over the last years, and it is expected that malignancies whose prevalence tends to increase with age will also increase in this population. Different malignancies in these patients have been reported over the past several years, but to our knowledge, our patient is the first pediatric case with papillary thyroid cancer and hemophilia.

Well-differentiated thyroid cancer (papillary or follicular) remains the most common endocrine cancer in the pediatric population. Thyroid cancer in children is associated with radiation exposure (associated with treatment or imaging of head and neck) [4]. It is believed that multiple imaging examinations to evaluate his cerebral hemorrhage was the most likely factor that caused his cancer development. In addition, cancer is more common in hemophilic patients and can be attributed to recurrent bleeds and inflammation (which stimulate the immune system), radiation exposure from multiple diagnostic imaging procedures, and chronic inflammation and immune dysregulation from multiple blood transfusions [5–7]. Hemophilia patients have been found to develop acquired chromosomal abnormalities. Recombinant products containing albumin have also been found to suppress lymphocyte transformation [8]. Another reason for the under-representation of cancers in hemophilia patients could be the refusal to undergo biopsies due to the risk of bleeding. After drainage of the subdural hematoma, our patient was followed for six years and received prophylactic factor VIII replacement treatment and antiepileptic drugs. Papillary thyroid cancer in children tends to be multifocal and multisegmental. Thus, total or near-total thyroidectomy is the recommended initial surgical procedure. Despite appropriate treatment, post-operative surgical site bleeding was observed, but inhibitory factors were negative. The patient was included in the high-risk thyroid cancer group, and after bleeding stopped, radioactive iodine and thyroid replacement therapy were planned. For recurrence control, ultrasound examinations and serum thyroglobulin monitoring are ongoing.

Conclusions

Finally, improved hemophilia care has extended the life expectancy of these patients, and cancer should be considered in patients with hemophilia. Hemophilia should not be used to rule out the possibility of a cancer diagnosis, and it should not be used to delay a diagnosis. These individuals should have access to appropriate treatment regimens and surgical procedures. Cancer incidence was found to increase in hemophilic patients,

and it should be kept in mind that hemophiliac patients may experience malignancies at any point in their life.

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Fibrocartilaginous dysplasia (fibrous dysplasia and massive cartilaginous differentiation): Case report and literature review

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Abstract

Fibrocartilaginous dysplasia (fibrous dysplasia and massive cartilaginous differentiation or fibrochondroplasia, FCD) is a rare variant of fibrous dysplasia and a term used for cases of fibrous dysplasia with prominent cartilage tissue. A limited number of FCD cases have been reported in the literature, which can be seen in both clinical forms.

A 16-year-old male patient, who had been followed for ten years with a diagnosis of polyostotic fibrous dysplasia in the left hip and cranium, presented with pain in the left leg after a fall. A subtrochanteric pathological fracture in the left femur was detected on exam, the lesion area was curetted, and osteotomy and fixation were applied. Microscopic assessment revealed a fibro-osseous lesion of benign spindle cell fibrous connective tissue with woven bone trabeculae, without osteoblastic rim or large areas of benign cartilage nodules. The final diagnosis was fibrocartilaginous dysplasia. In our literature review, 26 cases of FCD were reported so far. Age distribution of patients ranged from 4 to 53 years (mean 15.9) and the male / female ratio was 15/11 = 1.36. Eighteen cases were monostotic, and 8 were polyostotic. In cases with noted clinical and follow-up data, symptom duration ranged from 8 weeks to 18 years (mean 62.2 months), with no recurrence or malignant transformation in a mean follow-up of 21.71 (2-60) months post-treatment. In the cartilage component, there was increased cellularity, some nuclear atypia, binucleation, and myxoid degeneration. This situation simulates benign and malignant entities such as enchondroma, fibrocartilaginous mesenchymoma, well-differentiated intramedullary osteosarcoma, and chondrosarcoma with a differential diagnosis. FCD is a benign and very rare lesion with a prominent chondroid component, but may cause difficulty with differential diagnosis. Awareness of the histopathological and radiological features of FCD cases, their age range, and involvement areas provides an approach to distinguish them from lesions that may be confusing in a differential diagnosis.

Keywords: Fibrocartilaginous dysplasia, Fibrous dysplasia and massive fibrocartilaginous differentiation, Fibrous dysplasia, Fibrochondroplasia, Enchondral ossification, Chondrosarcoma

Introduction

Fibrous dysplasia (FD) is a dysplastic disorder of bone tissue characterized by woven bone structures that are randomly distributed, without an osteoblastic rim, within fibroblast-like spindle cell proliferation. It has been reported that GNAS1 gene mutations are found at a high rate in FD cases and play a role in their pathogenesis [1]. It has two clinical forms, monostotic and polyostotic. While the monostotic form is seen 8-10 times more frequently and may be asymptomatic, findings such as larger lesions, skin spots (café au lait), endocrine anomalies, and early puberty (McCune Albright Syndrome) are more common in the polyostotic form [2]. Although its exact prevalence is difficult to determine, given some asymptomatic cases, it accounts for approximately 5% to 7% of benign bone tumors [3].

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On microscopic examination, FD may present cementoid bodies, bleeding areas, secondary fibrohistiocytic proliferations, giant cell reactions, myxoid changes in stromal tissue, reactive bone areas of prominent osteoblastic rim, and cystic changes [1]. In addition, while microscopic cartilaginous differentiation can be found in approximately 10% of cases, cartilaginous matrix areas may be microscopically and radiologically dominant in rare cases [4, 5]. The terms "fibrous dysplasia and massive cartilaginous differentiation," "fibrocartilaginous dysplasia" (FCD), or "fibrochondroplasia" are suggested for these rare issues [1, 3, 6, 7]. We present a case who was followed for polyostotic fibrous dysplasia and operated on with a diagnosis of fibrocartilaginous dysplasia after a pathological fracture of the left proximal femur.

Case presentation

A 16-year-old male patient had calvarial thickening and ground-glass densities of the entire frontal bone as seen in a brain tomography 10 years ago; these findings are consistent with fibrous dysplasia. While he was followed with a diagnosis of polyostotic fibrous dysplasia in the left proximal femur and frontal bone, he was examined at our institution, with an operation plan a year ago. At that time, he had complaints of left hip pain and limping for 1 year. Physical exam revealed bilateral swelling on the frontal bone, and a café au lait spot with a size of 1 x 1 cm on the back. The radiological examination also revealed “Shepherd's crook” deformity of the left femur (Figure 1). Other physical findings were normal, with no signs of hyperthyroidism, hyperparathyroidism, hypercalcemia, or precocious puberty. The patient then presented with pain in the left leg after a fall. A subtrochanteric pathological fracture in the left femur was detected, so the lesion area was curetted, with osteotomy and fixation applied (Figure 2).

Figure 1: Antero-posterior radiograph of the left femur and classic shepherd's crook deformity

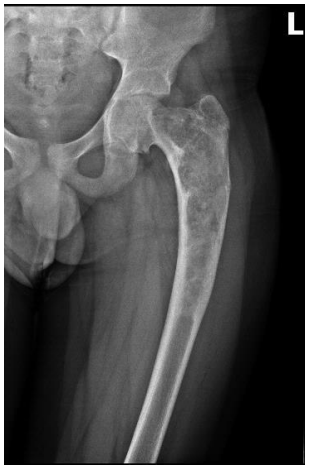
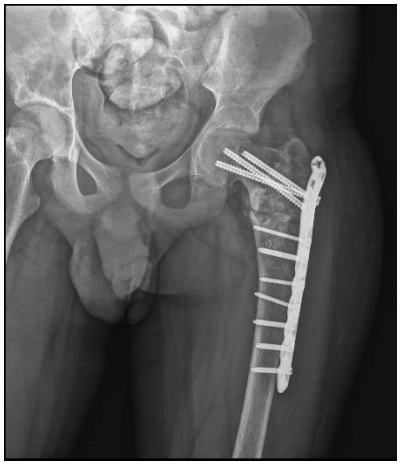


Figure 2: The radiological appearance of the lesional area after curettage, osteotomy, and fixation.



The patient’s operative specimen was macroscopically 7 x 7 x 4 cm in size, gray-brown, gray-white, and partly bone-hard. Microscopic examination revealed a fibro-osseous lesion of benign spindle cell fibrous connective tissue with woven bone trabeculae, without an osteoblastic rim (Figure 3) or large areas of benign cartilage nodules. The cartilaginous component was separated from areas of classical fibrous dysplasia with a distinct border, constituting 70% of the lesion (Figure 4). Hyperchromasia, atypia, increasing cellularity, and atypical mitosis were not observed either in the fibrous component or the cartilage nodules (Figure 5). The final diagnosis was fibrocartilaginous dysplasia, while informed consent was obtained from the patient’s family for scientific presentation.

Figure 3: Classical fibrous dysplasia area consisting of woven bone trabeculae (like Chinese letter) without osteoblastic rim within benign spindle cell fibrous connective tissue (H&E, 10X).

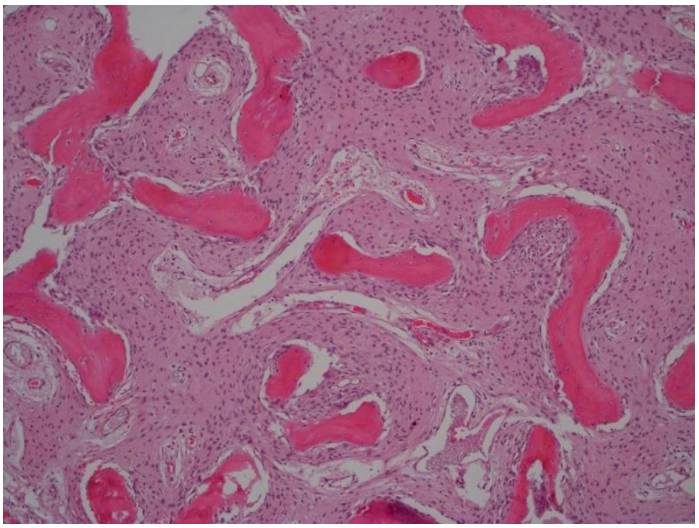


Figure 4: Classical fibrous dysplasia area and cartilage component separated by a distinct border (H&E, 4X).

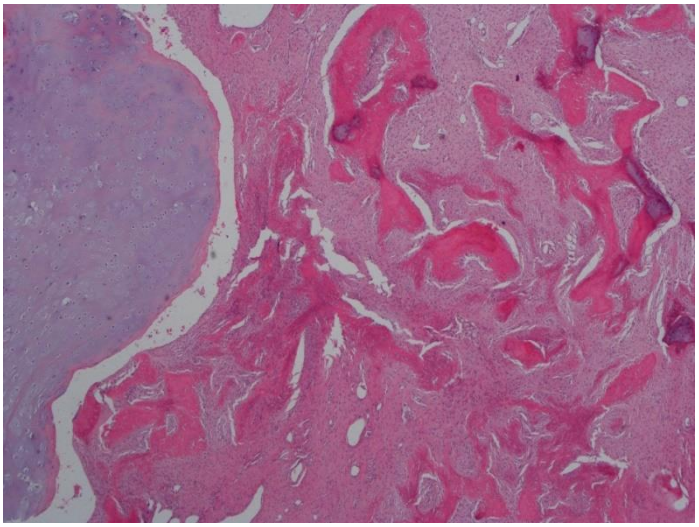


Figure 5: Enchondral ossification areas were observed around the cartilage nodules (H&E, 10X).

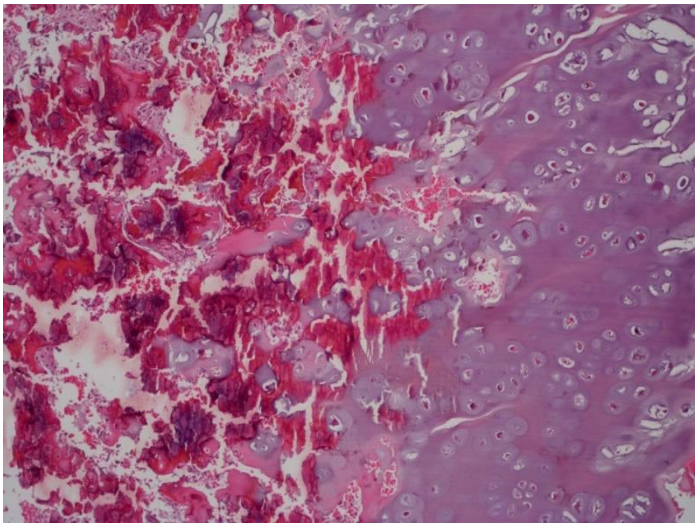


Table 1: Characteristics of reported FCD case

Case No. (reference)	Age	Gender	Localization	Type	Symptom	Symptom time	Follow-up
1. [7]	20	M	Proximal femur	P	Swelling	15 y	-
2. [5]	15	M	Femoral neck, tibia, fibula	P	Swelling, pain	7 y	-
3. [6]	23	F	Proximal tibia	P	-	-	-
4. [6]	8	F	Proximal femur	M	Pain	7 m	-
5. [6]	20	M	Proximal femur	M	Pain	-	
6. [6]	26	F	Ischiopubic bone	M	Swelling	8 y	
7. [6]	14	F	Proximal femur	M	-	-	
8. [6]	25	M	Proximal Femur	M	Pain, fracture	2 y	
9. [6]	4	M	Femoral shaft	M	Limping	-	
10. [4]	53	M	Proximal femur	M	Pain	10 m	-
11-18. [15]	8-18 (Mean: 11.3)	4 M 4 F	7 Femoral neck 1 Tibia diaphysis	8 M	Pain or fracture	-	-
19. [8]	21	M	Proximal femur, distal tibia	P	Pain, swelling, deformity	18 y	6 m
20. [14]	6	F	Femoral neck and proximal shaft	M	Pain	2 y	5 y
21. [13]	19	M	Proximal femur, distal fibula	P	Pain	3 m	1 y
22. [12]	8	F	Femoral neck	M	Pain, fracture	8 w	3 y
23. [11]	18	F	Femoral shaft, proximal radius and humerus	P	Pain	2 y	2 y
24. [9]	17	M	Proximal femur	M	Pain, swelling and progressive deformity	4 y	1 y
25. [10]	11	M	Proximal femur and skull	P	Pain, fracture	2 y	2 m
26. [17]	16	M	Right lower leg and foot	P	Tibial deformity, decreased mobility, and chronic pain	6 y	-
27. [Present case]	15	M	Proximal femur and skull	P	Pain, fracture	10 y	9 m

M: male, F: female, P: polyostotic, M: monostotic, y: year, m: month, w: week

Discussion

FCD is a rare variant of FD, and in our literature review, 26 cases have been reported so far (Table 1). This number is thought to be higher, due to the presence of incorrect or insufficiently described cases [8]. The age distribution of patients ranged from 4 to 53 (mean 15.9) and the male / female ratio was 15/11 = 1.36. Eighteen cases were monostotic, 8 were polyostotic, with the most common location of the lesions in the proximal femur (80%). The most frequent symptoms are pain, swelling, deformity, pathological fracture, and limping, all of which have been reported [3-15]. In cases with clinical and follow-up data, symptom duration ranged from 8 weeks to 18 years (mean 62.2 months), with no recurrence or malignant transformation observed in mean follow-up of 21.71 (2-60) months after treatment. Our case had similar characteristics to those reported in the literature, with no recurrence observed during the 9-month follow-up.

Focal fibrocartilaginous dysplasia (FFCD) cases in the literature may be confused with FCD, due to the similarity of names. FFCD is a rare benign disease of unknown etiology that tends to affect long bones in children. Histologically, it may exhibit a variety of patterns, from dense fibrous and tendon-like tissue to fibrocartilaginous tissue [16]. The presence of cartilage tissue is not an essential feature of FFCD diagnosis [16], with classical FD areas for diagnosis of FCD not found in reported FFCD cases.

Although FCD is considered a variant of FD, there are some differences and similarities. In addition, "Shepherd's crook" deformity on radiography for lesions of the proximal femur is known to be highly diagnostic of FD [2], but it should be noted that it may be seen secondary to metabolic, congenital, infectious, and traumatic conditions [9]. This finding is seen in many FCD cases in the literature [5, 7-9], and was present in our case. Unlike FD, the involvement of skull bones in FCD occurs less often, but was observed in one case [10]. In our work, calvarial thickening and ground-glass densities, which involve the entire frontal bone as detected in brain tomography 10 years ago, were accepted as compatible with FD.

A possible source of the cartilage component of FCD is thought to originate from cartilaginous rests near the growth plate, or callus tissue formed secondary to the fracture or coexisting enchondromatosis [4, 5]. However, no specific ratio or threshold value was determined. It was reported that cartilage areas in classical FD cases are usually smaller than 1 cm [6], using terms such as massive, extensive, prominent, dominant, large, and striking for the cartilage component in FCD [6, 8, 11-13, 15, 17]. However, in some cases, this ratio emphasizes that it constitutes the majority (60-85%) of the lesion [10, 11, 13, 14]. In our case, the cartilage component constituted approximately 70% of the lesion.

While classical FD areas constitute the fibrous component of FCD, we find in the cartilage component increased cellularity, some nuclear atypia, binucleation, or myxoid degeneration [6, 14]. This situation involves benign and malignant entities such as enchondroma, fibrocartilaginous mesenchyma, well-differentiated intramedullary osteosarcoma, and chondrosarcoma for a differential diagnosis [1, 3, 6, 14, 15]. The cartilage islands adjacent to the fibro-osseous component (typically FD) is the most important diagnostic clue to distinguish FCD from other cartilaginous neoplasms - such as enchondroma and chondrosarcoma [6]. Enchondral ossification areas, like the epiphyseal growth plate seen in the periphery of the cartilage islands, are generally not seen in conventional chondroid neoplasms [1, 6].

Fibrocartilaginous mesenchymoma (FCM) is a lesion easily confused with FCD clinically, radiologically, and histopathologically [8]. Although they were thought to be the same entities in the past, it is reported that they represent genetically different lesions [18]. FCM does not cause the gross distortion seen in FCD, can destroy the cortex and extend into the soft tissue, does not involve multiple bones, and spindle cells may demonstrate mild nuclear atypia and hyperchromasia as useful for a differential diagnosis with FCD [8]. Although bone production occurs in FCM, it is in the form of trabeculae formed by enchondral ossification at the periphery of cartilage masses surrounded by osteoblasts, unlike the characteristic woven bone trabeculae of FD [8].

The presence of coarse bony trabeculae, atypical nuclei, and mitosis versus the thin, branching woven bone trabeculae of FD, provides a guide in the differential diagnosis of FD versus low-grade intramedullary osteosarcoma [1]. Another method in differential diagnosis is to show GNAS1 gene mutation localized on chromosome 20. It was reported that the GNAS1 mutation is found in 50-70% of FD cases, playing a role in pathogenesis of FD [2], which supports the diagnosis of FCD [12]. In fibro-osseous lesions of the head and neck region, although there are few reported cases, GNAS1 mutations in FCM have not been demonstrated [18, 19]. Yet, it was reported recently that it can be found in 55% of parosteal osteosarcoma cases, but rarely in low-grade intramedullary osteosarcoma [19].

Treatment methods such as curettage of the lesion area, osteotomy, correction of deformity, and internal or external fixation are applied for the treatment of FCD [1, 12, 20]. Although a malignant transformation is rarely seen (less than 1%) in FD, there were none observed in any FCD case reported so far.

Conclusion

FCD is a rare benign lesion with a prominent chondroid component, so may cause difficulty with a differential diagnosis. The histopathological and radiological features of FCD cases, their age range, and involved areas should provide an accurate approach to distinguish them from lesions that may be confused with a differential diagnosis.

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A rare acute abdomen cause: intestinal perforation and invagination secondary to malignant melanoma metastasis

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Abstract

Malignant melanoma (MM) is a tumor with high metastatic potential. The small intestine is the third most common metastasis area for MM. Intestinal obstruction, intussusception, hemorrhage, and perforation have been determined as the clinical presentation in patients who were admitted to the hospital because of abdominal pain, weakness, constipation, weight loss, and palpable abdominal mass. Presentation as perforation is rarer than the other clinical presentations. We report the case of a patient with metastatic MM, who attended the emergency department because of acute abdomen. Perforation and invagination due to metastatic lesions were cured by surgical intervention. Possible metastasis should be considered in patients with active complaints or in patients scheduled for emergency intervention, as in our case, if there is a history of MM. Possible metastasis should be considered in preoperative planning, information, and anticipation of the operative procedure.

Keywords: Melanoma, Intestinal neoplasms, Intestinal perforation, Intestinal obstruction

Introduction

Malignant melanoma (MM) is a tumor with high metastatic potential. The small intestine is the third most common metastasis area for MM. However, only 5%–6% of patients with intestinal metastatic MM can be diagnosed based on a different clinical presentation [1]. MM in the small intestine usually presents as metastatic disease. In a review, 659 intestinal MM patients were analyzed. Primary small intestine MM was determined only in 16 (2.3%) cases [2]. In our literature review about intestinal MM, the clinical presentation was intestinal obstruction, intussusception, hemorrhage, and perforation in patients who were admitted to the hospital for abdominal pain, weakness, constipation, weight loss, and an abdominal palpable mass. Position emission tomography–computed tomography (PET-CT) scan is a main diagnostic approach [3]. Presentation as a perforation is rarer than the other clinical presentations. We present the case of a patient with metastatic MM who attended the emergency department due to acute abdomen.

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Informed Consent
The authors stated that the written consent was obtained from the patient presented with images in the study.

Conflict of Interest
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Case presentation

A 43-year-old male patient who was followed for MM that originated from the buccal region attended the emergency department due to abdominal pain and clouding of consciousness. During the emergency examination, tachycardia, sub-febrile fever, and blood pressure of 125/80 mm/Hg were observed. Guarding, rebound in all four quadrants, and general tenderness were noted upon examination. Emergency blood test results showed the following: white blood cells, 6000/mm³; C-reactive protein, 87 mg/L; creatinine, 1.2 mg/dL; and a mild imbalance of blood electrolytes. Multiple metastases were detected in bone and muscle tissue, in inguinal and axillary lymph nodes, and bilaterally in the lungs and brain on PET-CT scan, which had been performed 1 month before hospital admission (Figure 1). There was omental cake in the upper left quadrant, wall thickening in some intestinal segments, and extensive free fluid and air were detected on abdominal CT scan using an intravenous contrast agent, which was performed in the emergency department (Figure 2). The patient underwent surgery with a diagnosis of gastrointestinal tract perforation.

Figure 1: PET-CT image of patient showing metastatic lesions

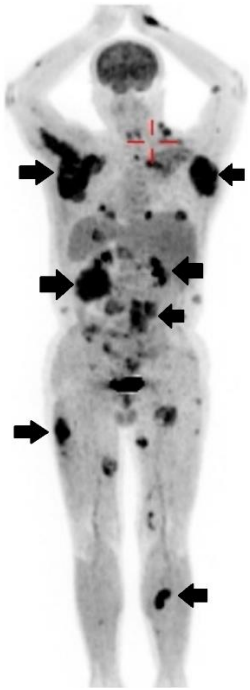
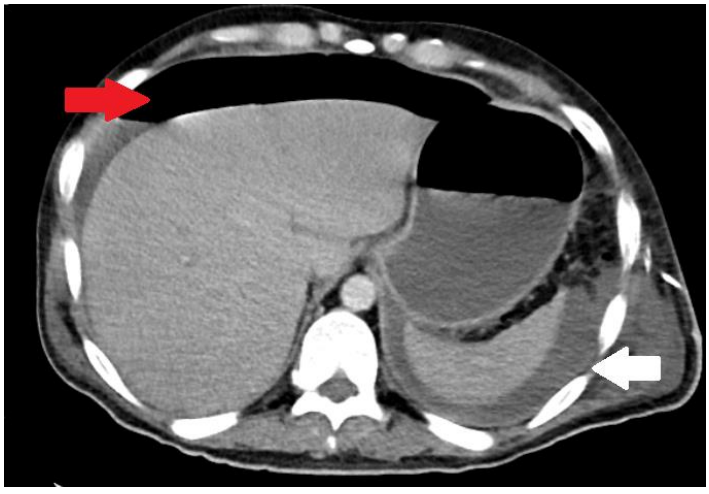


Figure 2: Abdomen CT image of patient. Red arrow shows subdiaphragmatic free air and white arrow shows perisplenic free fluid in abdomen



Extensive intestinal contents were detected in the abdomen during exploration. Tumor-related obstruction, tumor-related perforation, and tumor-related invagination were detected at 160, 180, and 200 cm, respectively, from the Treitz ligament. In the left upper quadrant, the tumoral mass, which was thought to have originated from the omentum, was observed (Figures 3, 4). The intervention was not planned for the tumoral mass due to its proximity to the spleen and pancreatic tail. After a 40-cm segment was resected, a double barrel ileostomy was opened. Surgery was terminated after lavation and debridement.

Figure 3: Omental tumor mass in the left upper quadrant

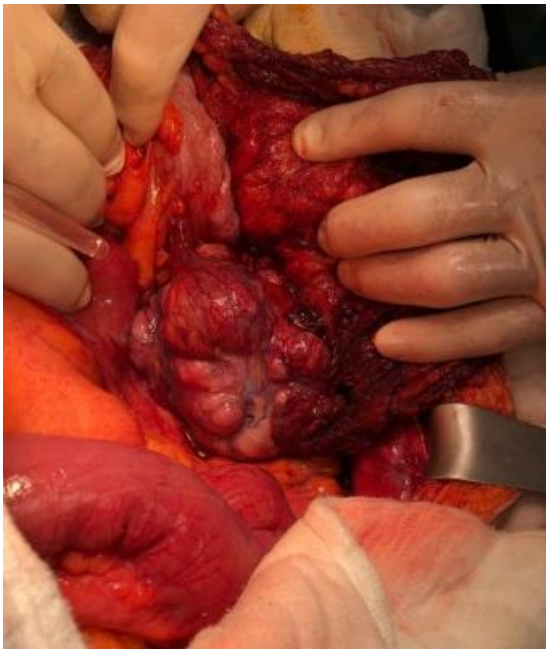
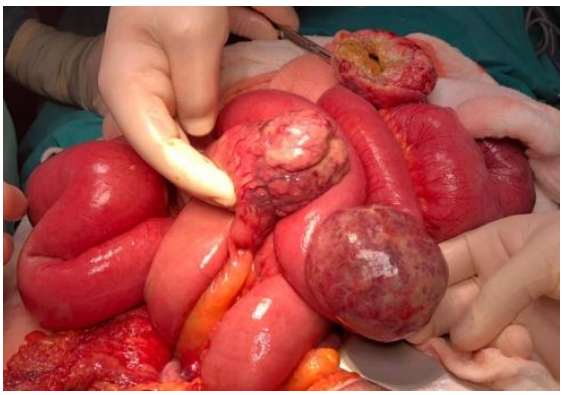


Figure 4: Obstructed, invaginated, and perforated intestinal segments due to metastasis



During the postoperative period, the patient was taken to the intensive care unit for follow-up because he was intubated. Significant acidosis and hypoxia were detected in the arterial blood gas. Electrolyte imbalances and an increase in infection parameters and creatinine levels were detected. The patient, who was under intensive positive inotrope treatment, died due to cardiac arrest on postoperative day 1. After pathological examination, MM metastasis was diagnosed in the resected intestinal segments.

Discussion

MM is a malignancy with a high potential for metastasis in the gastrointestinal tract. Most metastatic lesions are discovered during screening after active complaints or during postmortem examinations. When metastatic lesions have a polypoid character, they may pose a risk for intussusception [1].

Intestinal metastasis was found in 60% of patients who died due to melanoma, and pre-mortem diagnosis was made in only 1.5%–4.4% of patients [3]. MMs with a superficial spread tend to have more intestinal metastasis than the other types of MMs [4]. The prognosis of patients with primary small bowel MMs is worse than for those with intestinal metastasis [5]. Wedge mesenteric resection for lymph node excision is the recommended treatment together with segmental small bowel resection with clean distal and proximal surgical margins [6]. Excision of all metastatic lesions has a positive effect on prognosis in patients with possible intestinal metastatic MM [3]. Possible metastasis should be considered in patients with active complaints or in patients scheduled for emergency intervention, as in our patient, if there is a history of MM.

Conclusions

Physicians who follow-up MM patients should consider abdominal pain in MM patients to be an alarming symptom that may be a sign of abdominal metastasis. Surgeons who encounter MM patients with abdominal pain in the emergency department should be aware of complications associated with abdominal pathology that are relevant to MM. Possible metastasis should be considered in preoperative planning, information, and anticipation of the surgical procedure.

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Intraoral route for excising a large dermoid cyst of the floor of mouth: A discussion

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Abstract

Surgical excision is an effective treatment for a dermoid cyst (DC) of the floor of the mouth (FOM). A dichotomy of opinions exist regarding the appropriate approach to surgical excision. In this study, we discuss our experience with excising a large DC via an intraoral route. An 18-year-old female presented with swelling of the submental region for one year. Under general anesthesia, an incision was conducted in the mucosa of FOM. By removing some contents, the cyst was delivered in toto. While some studies have stressed that the location of origin and size of the DC influence the route of excision, other authors have pointed out that by the time both median genioglossal and geniohyoid cysts become large enough to produce symptoms, both the muscles are splayed out and thus, the cysts are more amenable to excision by intraoral approach. This case highlights a dichotomy of opinion regarding the existing literature and to educate the clinicians about the benefits of the intraoral route of excision.

Keywords: Dermoid cyst, Mouth floor, Cysts, Submental, Intraoral, Extraoral

Introduction

Dermoid cyst (DC) of the floor of the mouth (FOM) is an uncommon entity, and surgical excision is the only effective treatment for DC. A classical study described 1495 cases of DC, in which only 1.6% were located in the FOM [1]. There is a dichotomy of opinion regarding the appropriate approach to surgical excision. Some surgeons prefer the extraoral approach, via a submental incision; whereas others favor the intraoral route, via the mucosal incision. From our experiences, the extraoral approach leads to a visible submental scar or even worse, a hypertrophic scar. We prefer excising all submental DCs, even large ones via the intraoral route [2, 3]. We present our experience in the case below.

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Case presentation

An 18-year-old female presented with painless diffuse swelling of the submental region over the last year, giving her a "double chin" appearance (Figure 1, 2). The swelling slowly increased in size, and for the last two months, it had started to protrude in the FOM (Figure 3). On bimanual palpation, a well-defined, non-tender, cystic swelling of approximately 8 x 6 x 6 cm in size was detected in the midline, which was free from the mandible.

Figure 1: View of submental swelling

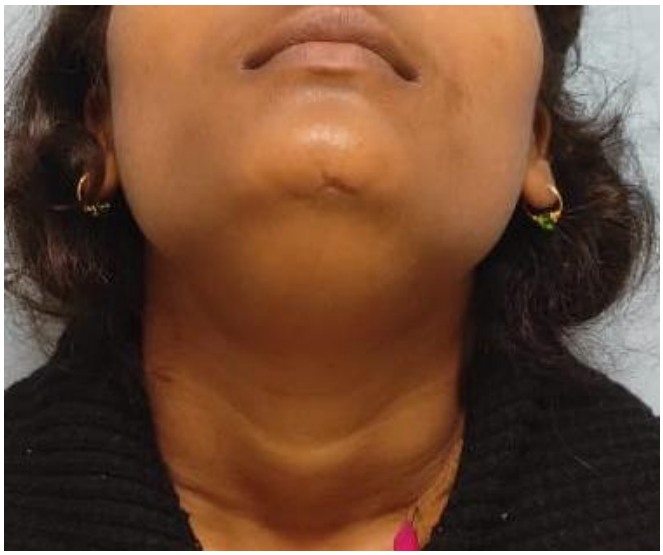
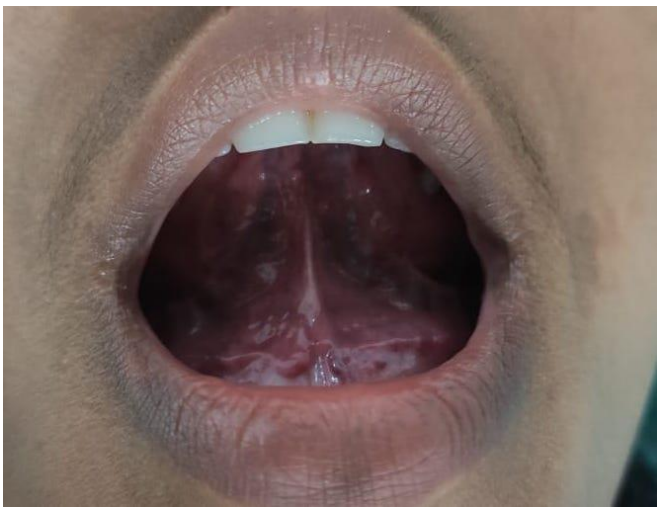


Figure 2: Lateral view showing the submental swelling

Figure 3: Intraoral view showing the submental swelling



Magnetic Resonance Imaging revealed a well-defined midline cystic lesion that had displaced bilateral geniohyoid muscles and measured 73 x 50 x 48 mm. Mild enhancement along the cyst wall is noted.

Consent was obtained for surgical intervention, for taking photographs, and for publication of photographs. Nasotracheal intubation was used to induce general anesthesia and patient was positioned supine. One shot of intravenous antibiotic was given. A tongue stitch was taken, and the tongue was retracted out of the field. An incision was conducted at the right side of the frenulum to protect the Wharton's ducts. A combination of blunt and sharp dissection was performed, using scissors, curved artery forceps, and bipolar electrocautery. The application of traction and counter-traction forces assisted in the dissection. As it is challenging to deliver the broadest part of the cyst, a stab incision was given, and some of the cheesy contents were evacuated (Figure 4). This procedure aided in excising the rest of the DC, out of the surrounding muscles. A 75 x 55 x 50 mm-lesion was dissected. (Figures 5, 6). Hemostasis was achieved, and closure was done with absorbable sutures. The operating time was 70 minute.

Figure 4: MRI showing a well-defined cystic lesion (Arrow), displacing geniohyoid muscles, and measuring 73x50x48 millimeter

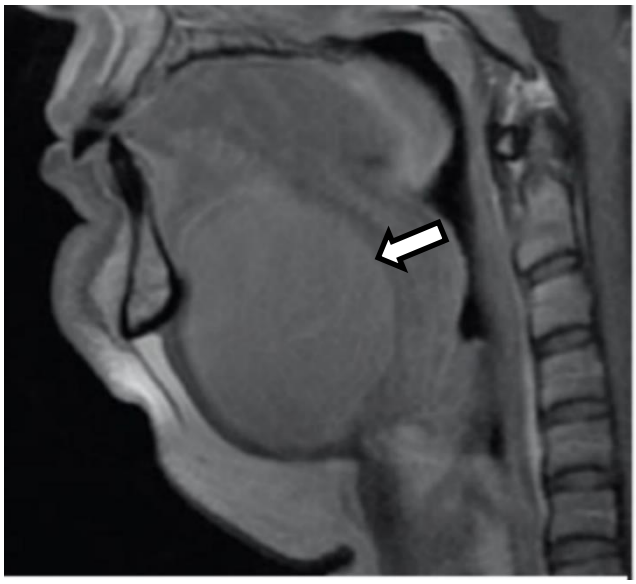


Figure 5: Partial excision of the swelling via intraoral route. A stab incision had to be applied and some contents had to be evacuated to help in delivery of the cyst.

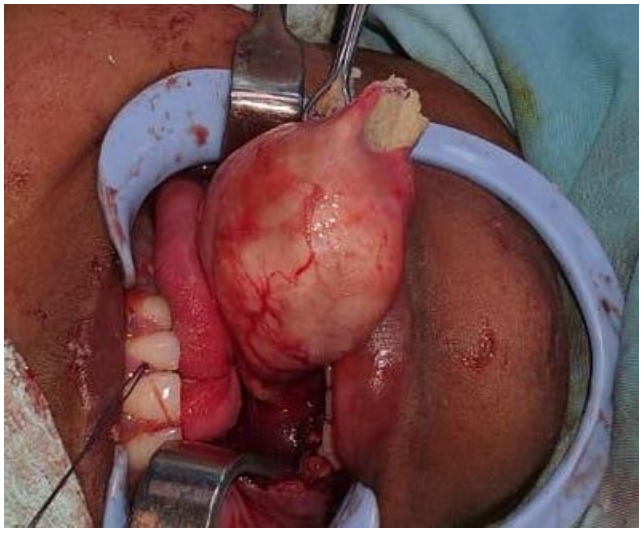
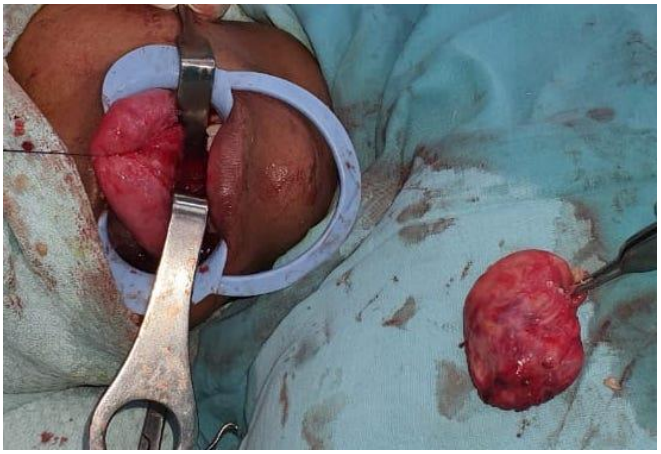


Figure 6: After complete excision of the cyst and hemostasis

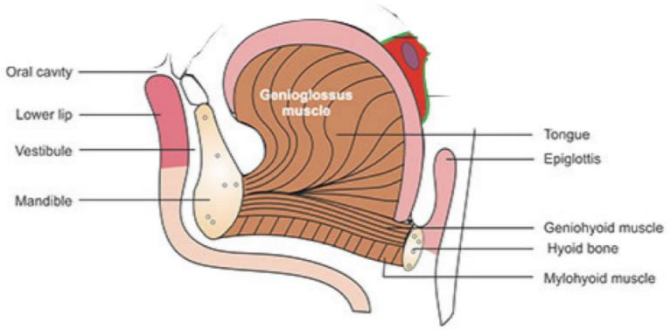


Histopathological examination confirmed the diagnosis of a dermoid cyst. In the postoperative period, edema developed in the submental region, which resolved with conservative methods.

Discussion

DC is a clinicopathological lesion of developmental origin. Even though it is congenital, DC usually present in the second or third decade, when they become sufficiently large to cause symptoms due to mass effect [4]. The anatomy of the FOM is depicted in Figure 7. The median DC may rest on the mylohyoid and spread the geniohyoid, called geniohyoid DC, or may rest on the geniohyoid and spread the genioglossus, called genioglossal DC [5]. Geniohyoid DC may present as double chin; whereas genioglossal DC presents as sublingual swelling, which may lead to articulation and mastication disorder, and rarely causes dysphagia, dysphonia, and dyspnea [2]. Large cysts may result in a combination of symptoms, as was in our case.

Figure 7: Relevant anatomy of floor of mouth



Many surgeons believe that the origin of the DC and size of the cyst influence the route of extirpation. Longo et al. [6], Teszler et al. [7] and other studies recommended excision using the intraoral route for small genioglossal cysts. However, these studies preferred the extraoral route for a geniohyoid cyst or large sublingual cyst.

However, some surgeons favor the intraoral route, irrespective of the location and size of the lesion- Ohta et al. [4], Brusati et al. [8] cite the following reasons for favouring the intraoral route. Sewart [2] points out that a large cyst, which causes symptoms, should involve the median septum between genioglossus and geniohyoid muscles. The difference in surgical approach, advocated by the previously mentioned surgeons, is based more on theory and not practicality. Meyer et al. [9] and Sewart [2] concede that all DC (of any subtype) originate from above the mylohyoid. Hence, the plane below mylohyoid should not be violated, thus necessitating excising all median DC via the mucosal route.

Sewart [2] and Walstad et al. [3] reiterate that, with patience, extensive cysts can be removed via the intraoral route. We also performed the same operation, completed the dissection, and excised the cyst in toto. In massive cysts, some contents can be aspirated to reduce the volume and deliver it through mucosal incision [7]. Brusati et al. [8] stated that an extended midline mucosal incision is sufficient for the excision of tumors as distant as the posterior third of the tongue and the cervical spine. Thus, the extended midline mucosal incision can remove large cysts of FOM, even if they reach up to the hyoid bone.

Incising through the skin, platysma, and mylohyoid to reach cysts, does not seem justified to us. Wider surgical exposure and better visualization of structures do not balance the outcome for an unaesthetic scar. The scar may become hypertrophic and appear as a patch of alopecia in males. The best scar therapy is prevention. In exceptional conditions such as an inflamed lesion, that is expected to be adherent to surrounding structures or sizeable blood vessels passing in the vicinity of the lesion, adopting an extraoral approach appears prudent [2].

In conclusion, we advocate the intraoral approach for excising DC of FOM. We wrote this piece to highlight the conflict in the existing literature and to educate the clinicians regarding the benefits of an intraoral approach.

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