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EDITORIAL

Dear colleagues,

The subjects covered in this issue of the Journal of Comprehensive Surgery are diverse and mirror the changing surgical landscape.

Our collection of distinctive case studies provides insights by sharing clinical experiences that not only spark discussion but also deepen our comprehension of the complex nature of surgical operations.

We examine the urgent problems related to gastrointestinal bleeding this time. We closely examine the literature to offer a perspective that can assist you in making knowledgeable therapeutic decisions in this intricate field.

We also examine contentious surgical topics, such as talks about congenital breast deformities. To make sure that our publication continues to be a strong forum for important discourse in the surgical community, it all comes down to accepting different points of view.

Feel free to peruse through this issue. Each article contributes a piece to our journey towards excellence in surgical practices.

Best regards,

Assoc. Prof. Alparslan KOÇ M.D.
Editor-in-Chief

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Evaluation of clinical and laboratory parameters of patients with the diagnosis of upper gastrointestinal system bleeding

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ABSTRACT

Aims: In this study, it was purposed to evaluate demographic, clinical, laboratory characteristics, bleeding etiologies, risk factors, comorbidity and mortality of the patients who were interned with the diagnosis of upper gastrointestinal system bleeding.

Methods: In this study, 157 patients those hospitalized to Ministry of Health Beyoğlu Public Hospitals Association Gaziosmanpaşa Taksim Training and Research Hospital Internal Medicine Clinic with the diagnosis of upper gastrointestinal bleeding between 1 April 2014 and 1 April 2015 were evaluated retrospectively. Age, gender, duration of hospitalization, comorbidity, prescription story, need and amount of transfusion, endoscopic findings, hemoglobin (Hgb), blood urea nitrogen (BUN), urea, creatinine (Cr) values on admission, complication and mortality data were recorded. IBM SPSS (Statistical Package for Social Sciences) for MAC 21.0 program was used for statistical analysis in order to evaluate the data.

Results: Patient were aged between 17 and 94 .The mean age was 59.04±20.55. 95 (68.35%) of patients were male and 44 (31.65%) were female with the male/female ratio of 2.15/1. While 64.75% of the patients in our study had at least one additional disease, no additional disease was detected in 35.25%. Endoscopic procedure was peformed 89.93% of patients for both diagnosis and treatment. Exitus was seen in 7 patients and mortality was detected as 5.04%. Median age of deceased patients was 75.28±15.39. Median age of surviving patients was 58.18±20.47.

Conclusion: Our study revealed that upper GI bleeding is an important cause of mortality and morbidity despite advanced treatment options and intensive care conditions. The most important risk factors responsible for mortality are advanced age and the presence of comorbidities, as seen in our study.

Keywords: Upper gastrointestinal system bleeding, duodenal ulcer, endoscopy

INTRODUCTION

The upper gastrointestinal (GI) system bleeding is defined as bleeding from the gastrointestinal segment proximal to the ligament of Treitz, including the esophagus, stomach, and duodenum. It is categorized as varicose and non-variceal bleeding. Upper GI bleeding is responsible for 67 hospital admissions per 100,000 population annually in the USA and has an inpatient mortality rate of 1.9% in a tendency to decrease recently.[1] The most common causes of upper GI bleeding are peptic ulcer disease and esophageal varices.[2] Patients with upper gastrointestinal tract bleeding may present with minor or subclinical symptoms, or they may have a fulminant course. Approximately 80% of bleeding stops spontaneously, while 20% continues or recurs.[3,4] Some clinical parameters such as age, comorbidity, hemodynamic status, hematemesis and hematochezia are important risk factors that increase the risk of mortality.[5-7]

In our study, we aimed to evaluate the demographic characteristics, clinical and laboratory parameters, bleeding etiologies, risk factors, morbidity and mortality by retrospectively scanning the files of patients who were interned and followed up with a diagnosis of upper GI bleeding in the internal medicine clinic between 1 April 2014 and 1 April 2015.

METHODS

In this study, 157 patients who were hospitalized with a diagnosis of upper GI bleeding in the internal medicine clinic of Ministry of Health Beyoğlu Public Hospitals Association Gaziosmanpaşa Taksim Training and Research Hospital between 1 April 2014 and 1 April 2015 were evaluated retrospectively. 18 patients were excluded from the study due to missing data in their files. Data about age, gender, duration of hospitalization, presence of additional diseases, history of drug use [acetyl salicylic acid (ASA), oral anticoagulant (OAC), non-steroidal anti-inflammatory drug (NSAID)], need and amount of transfusion, endoscopy findings, arrival hemoglobin, blood urea nitrogen (BUN), urea and creatinine (Cr) values, complications and exitus development of patients were recorded. Using these data, the demographic characteristics of the patients, length of stay, comorbidities, complications, mortality rates, BUN/Cr, urea/Cr ratios, drug use rates and medications used were investigated. Rate of endoscopic procedures, transfusions and relationship between age-mortality, and age-length of hospital stay were also analyzed. The study was carried out with the permission of the Ministry of Health Beyoğlu Public Hospitals Association Gaziosmanpaşa Taksim Training and Research Hospital. We obtained an informed consent form from all patients for procedure. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Ethics committee approval was not required at that time.

Statistical Analysis

IBM SPSS (Statistical Package for Social Sciences) for MAC 21.0 program was used for statistical analysis while evaluating the data obtained in the study In addition to descriptive statistical methods (Mean, standard deviation, frequency), Student's t test was used for two groups in normally distributed parameters in the comparison of quantitative data and Mann Whitney U test was used to compare two groups of parameters those do not have normal distribution. Oneway Anova test was used for comparisons of normally distributed parameters between more than two groups. Oneway Anova test was used for comparisons of normally distributed parameters between more than two groups. Kruskal Wallis test was used in comparisons between more than two groups of parameters those do not have normal distribution, and Mann Whitney U test was used to determine the group giving rise to discrepancy. Pearson R correlation was used to examine the relationships between continuous variables. Z test was used to compare percentage values. All analyzes were performed two-tailed.

RESULTS

7.19% of the cases are between the ages of 17-25, 21.58% are between the ages of 26-45, 27.34% are between the ages of 46-65, and 43.88% are over the age of 65. 31.65% of the cases are female and 68.35% are male. The male/female ratio is 2.16. 35.25% of the cases have no comorbidities, 64.75% have at least one comorbidity. 30.94% of the cases have a history of drug use (ASA, OAC, NSAID), while 60.94% don't. Complications developed in 13.67%, any complications did not develop in 83.33% of the cases (**Figure 1**).

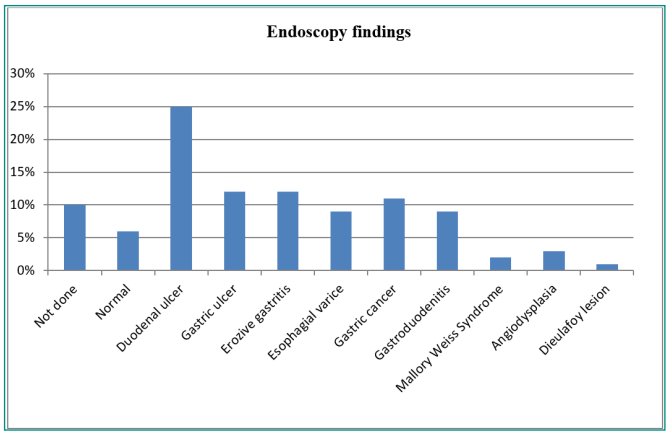

Figure 1. Percentage distribution of endoscopy findings of cases

Complications were observed in older patients, p>0.05. One patient was complicated with perforation and referred to surgery. That patient was male and 56 years old. He was hypotensive and his hgb value was 8.4 gr/dl on admission. His endoscopic finding was gastric cancer. He did not have any other comorbidity. He died on post operative second day due to septic schock. 94.96% of the cases were alive, 5.04% died. 70.50% of the cases were transfused and 29.50% of the cases were not (**Figure 2**).

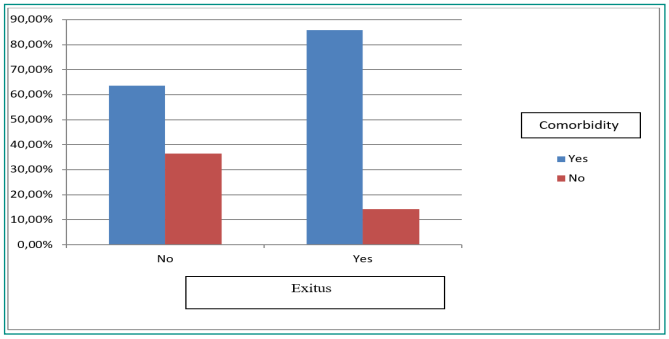

Figure 2. Comorbidity rates by death and survival (p>.200)

Mean transfusion amount was 2.09±2.01 units (Min: 0, max: 14.00). All patients were treated with intravenous (IV) and proton pump inhibitors (PPIs) ampirically. Patients with known or newly detected esophagial/gastric varices were applied somatostatin infusion. Endoscopy was performed in 89.93%, while endoscopy was not performed in 10.07% of the cases. Duodenal ulcer was most commonly detected finding endoscopically in 25% of the cases. General characteristics of the cases are shown in **Table 1** and endoscopic findings are shown in **Figure 1**.

Mean values of age, length of stay, hgb value, BUN/Cr ratio, transfusion amount according to endoscopy findings are illustrated in **Table 2** and in pairwise group comparisons, it was observed that patients with doudenal ulser findings stayed in the hospital for a shorter period of time than patients with gastric cancer findings, (p= 0.003).

Table 1. General characteristics of cases with upper GIS bleeding

		N	%
Age	17-25	10	7.19
	26-45	30	21.58
	46-65	38	27.34
	>65	61	43.88
Gender	Female	44	31.65
	Male	95	68.35
Length of hospital stay (day/s)	1-5	75	53.96
	6-10	43	30.94
	11-20	17	12.23
	>20	4	2.88
Comorbidity	No	49	35.25
	Yes	90	64.75
Drug use (ASA, OAC, NSAID)	No	96	69.06
	Yes	43	30.94
Complication*	No	120	86.33
	Yes	19	13.67
Schock		6	4.31
CV¶		8	5.75
ARF		1	0.71
EUHD		-	-
Rebleeding$^{\Delta}$		3	2.15
MT$^{\varepsilon}$		1	0.71
Perforation		1	0.71
Exitus	No	132	94.96
	Yes	7	5.04
Endoscopic procedure	Not done	14	10.07
	Done	125	89.93
Blood transfusion	Not done	41	29.50
	Done	98	70.50

Abbrevetions: ASA, acetyl salicylic acid; OAC, oral anticoagulant; NSAID, non steroidal anti inflamatory drug; CV, cardiovascular; ARF, acute renal failure; EUHD, exacerbation of underlying hepatic disease; MT, massive transfusion
*Complications are defined as schock requiring positive inotropics, acute coronary syndrome, arrhythmia, stroke, acute renal failure, rebleeding, exacerbation of underlying hepatic disease, massive transfusion and perforation.
¶ CV complications are defined as acute coronary syndrome, arrhythmia and stroke.acute renal failure.
$^{\Delta}$ Rebleeding is defined as observation of second event bleeding signs after clinical and/or endoscopic stabilization of initial bleeding during hospitalization.
$^{\varepsilon}$ Massive tranfusion is defined as ≥10 units/24hours erythrocyte suspension.

Table 2. Mean values of age, length of stay, hgb value, BUN/Cr ratio, transfusion amount according to endoscopy findings

Endoscopy finding	Age	Length of stay (Days)	Hgb (gr/dl)	BUN/Cr ratio	Transfusion (Number of units)
Not done	66.64	5.57	9.72	44.27	1.50
Normal	60.00	6.50	11.06	29.42	0.87
Duodenal ulcer	46.97	4.40	9.37	32.27	2.17
Gastrik ulcer	61.05	6.23	9.18	45.24	1.76
Erozive gastritis	64.47	7.47	8.55	44.31	2.41
Esophageal varice	54.75	7.75	7.81	32.62	2.08
Gastric cancer	68.33	11.00	8.45	45.68	3.06
Gastroduodenitis	58.41	6.58	9.14	36.03	1.91
Mallory Weiss Syndrome	66.33	5.33	8.90	42.20	3.00
Angiodysplasia	74.25	7.50	9.35	21.45	1.75
Dieulafoy lesion	68.50	4.00	8.35	31.00	3.00

In pairwise group comparisons, it was observed that patients with doudenal ulser findings stayed in the hospital for a shorter period of time than patients with gastric cancer findings, p = 0.003

Distribution of duodenal or gastric ulcers in their own group with respect to Forrest Classification was as following; 3 (5.8%) cases were Class 1B, 4 (7.7%) cases were Class 2A, 14 (26.9%) cases were Class 2B, 5 (9.6%) cases were Class 2C and 26 (50%) cases were Class 3. No Class 1A ulcer was detected. Class 1B to Class 2A was intervened with epinephrine injection during endoscopic procedure. 10 (83.7%) of 12 esophageal varice cases were treated with endoscopic band ligation, also. The median age of deceased patients was determined to be 80 (min: 56, max: 94) (**Figure 3**).

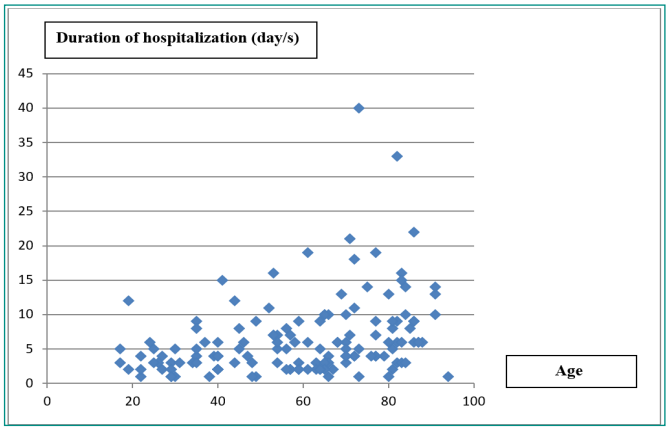

Figure 3. Duration of hospitalization according to age

The median age of surviving patients was found to be 62 years (min:17, max:91). There was a statistically significant difference between the two groups (p=0.040) (**Table 3**). In our study, the rate of comorbidities was 63.63% in those who survived, the rate of comorbidities was found to be 85.71% in those who deceased. However, no significant difference was found in the percentage of comorbidities according to mortality (p>0.200). Mean time from hospitalization to death was 8.14±11.81 (min:1, max:33) in exitus group. Mean values of age, time to outcome, hgb, and transfusion amount of complicated and died patients are shown in **Table 4**. The Mann-Whitney test showed that exitus group BUN/Cr ratio was higher, U=193.00, p=0.010. A similar effect was seen in Urea/Cr ratio, U=202.00, p=0.012.

Table 3. Mean/median ages of surviving and deceased patients

	Mean±SD	Median	Minimum	Maximum
Surviving patients	58.18±20.47	62	17	91
Deceased patients	75.28±15.39	80	56	94
Total	59.04±20.55	63	17	94

The Mann-Whitney U test showed that there was a significant age difference between the two groups, (U = 249, p = 0.040).
Abbrevetions: SD, standard deviation.

Table 4. Age, time to outcome, hgb, and transfusion values of complicated and died patients

	Complications			Excitus		
	Mean	Min	Max	Mean	Min	Max
Age	76.31±14.11	40	94	75.28±15.39	56	94
Time to discharge or death	8.52±8.26	1	33	8.14±11.81	1	33
Hgb (gr/dl)	9.18±1.87	6.70	14.00	8.90±2.42	6.70	14.00
Transfusion (number of units)	3.57±2.89	,00	14.00	2.14±1.21	,00	4.00

The presence of complications had no effect on BUN/Cr or Urea/Cr ratios, p>0.100. No effect of drug use was observed on these values, p>0.200 (**Table 5**). Hemoglobin values were not statistically significant in any subgroups, p>0.05. No statistically significant relationship between transfusion and mortality was observed, p>0.005.

Table 5. Mean values of BUN/Cr and UREA/Cr ratios in relation to exitus and complication status

			BUN/Cr	UREA/Cr
Exitus	No	36.79	78.18	91
	Yes	61.98	132.38	91
Complication	No	37.10	78.58	94
	Yes	44.14	95.65	94
Drug use	No	35.88	76.74	94
	ASA	55.61	116.21	94
	OAC	33.74	71.74	94
	NSAID	38.22	80.29	94

DISCUSSION

In our study, it was determined that the patients who were admitted to the clinic due to upper GI bleeding were mostly older, with comorbidities, and male patients. The ages of the patients range from 17 to 94. The mean age of the patients was determined as 59.04±20.55.

Majority of patients were over age of 65 with a rate of 43.88%. Only 7.9% of the patients were between the ages of 15-25. There are studies in the literature supporting that upper GI bleeding occurs in older ages. In their study on 2196 patients with upper GI bleeding, Wollenman et al.[8] found the average age of the patients to be 52, and in our country, Bahadır et al.[9] found it to be 59.91+7.5. It is thought that the increasing frequency of diseases such as coronary artery disease, cerebrovascular disease, osteoarthritis, which will increase the use of aspirin, NSAIDs and anticoagulant drugs, and additional diseases such as chronic liver disease, chronic renal failure and GI malignancies are effective in the higher incidence of upper GI bleeding in older ages. 95 (68.35%) of the patients were male and 44 (31.65%) were female, and the male/female ratio was 2.15/1. In studies on upper GI bleeding in the literature, the male/female ratio is close to that in our study.[10,11] While 64.75% of the patients in our study had at least one additional disease, no additional disease was detected in 35.25%. There are studies in the literature indicating that upper GI bleeding is often accompanied by additional diseases.[12,13]

Endoscopy was performed in 89.93% of the patients in our study for diagnosis and treatment purposes, and in 14 patients, 10.07%, it could not be performed due to reasons such as improper clinical conditions such as arrhythmia, acute coronary syndrome, respiratory failure, technical problems in the endoscopy unit and the patient's refusal to accept the procedure. In the literature, the rates of endoscopy in patients hospitalized with upper GI bleeding are close to those in our study. Longstreth et al.[10] found a 93.4% rate of endoscopy in their study. In our study, there was no Forrest Class 1A case and distribution of other groups was in favor of Class 3 incompatible with the literature.[14] This discrepancy could be explained in a way that in our clinics there was a tendency for endoscopic procedures to be performed after clinical stabilization enough to be considered elective.

Exitus occurred in 7 of the cases in our study during hospitalization and the mortality rate was found to be 5.04%. In the literature, the mortality rate varies between 3% and 14%.15 It was found to be 4.9% in the study of Tuncer et al.[16], 5.1% in the study of Kasap et al.[17], and 12.1% in the study of Bayır et al.[18] in patients presenting to the emergency clinic. It is thought that the mortality rate in our study is close to the lower limits of the range given in the literature because the patients included in the study consisted of patients who were admitted to the clinic after being evaluated in the emergency department.

In our study, the average age of the patients who died was 75.28±15.39, and the average age of the patients who survived was found to be 58.18±20.47, and it was considered statistically significant, p=0.040. The relationship between mortality and age in the literature is consistent with that in our study.[19]

Study Limitations

In our study, the rate of comorbidities was found to be 63.63% in those who survived, while the rate of comorbidities was found to be 85.71% in those who died, However, no significant difference was found in the percentage of comorbidities according to mortality (p>0.200). In our study, although the rate of comorbidities in the mortality group was higher than that in the survival group, it was not statistically significant due to the fact that there were not a sufficient number of patients in the mortality group.

CONCLUSION

Our study revealed that upper GI bleeding is an important cause of mortality and morbidity despite advanced treatment options and intensive care conditions. The most important risk factors responsible for mortality are advanced age and the presence of comorbidities, as seen in our study.

The most common causes of upper GI bleeding are peptic ulcer disease and esophageal varices. The approach to a patient presenting with acute upper GI bleeding should be to first evaluate the patient's hemodynamic status and ensure stabilization. The next step should be to identify the bleeding site, ensure bleeding control, and prevent rebleeding. Patients of advanced age and comorbidities, and those with hemodynamic instability such as shock, orthostatic hypotension, or active bleeding symptoms should be monitored in intensive care conditions where vital signs can be closely monitored.

The main etiological factors in the formation of peptic ulcers, which are responsible for a significant portion of upper GI bleeding, are H.pylori, acetyl salicylic acid and other NSAID use. Thus situated, unnecessary and carelessly use of aspirin and NSAIDs should be avoided, and when there is a medical indication for their use, protective measures such as acid suppressive treatment and H.pylori eradication should be taken.

For esophageal variceal bleeding, which is another important cause of upper GI bleeding, essential precautions against chronic liver disease (such as campaign alcohol, obesity and hepatitis virus transmission) should be taken in the primary care setting, primary and secondary prophylactic measures against bleeding should also be taken in patients with portal hypertension and associated varicose veins.

ETHICAL DECLARATIONS

Ethics Committee Approval: This article is a publication of the internal medicine specialty thesis of Mehmet Akif Tükenmez, which was completed in 2015. Since the study is produced from a thesis in 2015, ethics committee approval is not required.

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

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

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

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Prognostic factors and survival of breast cancer in patients over 40 years of age

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ABSTRACT

Aims: Breast cancer is the cancer with the highest incidence and mortality in women. There are differences in prognosis and survival between women over and under the age of 40. In this article, we aimed to examine breast cancer prognostic factors and survival results in people over the age of 40.

Methods: 1187 patients aged 40 and over who underwent surgery at the Ondokuz Mayıs University Department of General Surgery between August 2005 and April 2019 and whose data were accessible were retrospectively examined. Data were obtained from the hospital automation system, the Ministry of Health's online database, hospital archives, patients, and/or their relatives. They were classified separately in terms of type of surgery, axillary metastasis status (according to radiological status if axilla surgery is not performed), type of axilla surgery performed, pathological tumor size, number of pathological lymph nodes, pathological stage, lymphovascular and perineural invasion status, hormone receptor positivity, C-erb B2 and Ki-67 status, neoadjuvant treatment status, and molecular subgroup. Variables were analyzed individually for recurrence, mortality, and survival. Results found to be significant were subjected to multivariate analysis testing. Statistical significance was accepted as $p<0.05$.

Results: As a result of multivariate analysis performed by excluding data that disrupted homogeneous distribution, perineural invasion, lymphovascular invasion, grade, and progesterone receptor status were determined to be independent prognostic factors in terms of recurrence. Lymphovascular invasion and progesterone receptor status were found to be independent prognostic factors for mortality.

Conclusion: A lot of studies have been conducted, and criteria have been determined for breast cancer prognosis and survival. In our results, lymphovascular invasion and progesterone receptor status were found to be independent prognostic markers for both recurrence and mortality. More reliable results can be obtained with prospective study analyses.

Keywords: Prognostic factor, survival, breast cancer

INTRODUCTION

According to data from the World Health Organization, breast cancer is the most common cancer in women, both in the world and in Türkiye, and causes the highest mortality. This result was found to be the same for women over 40 years of age.[1] Therefore, prognostic factors and the survival of breast cancer gain importance.

Breast cancer treatment is constantly being renewed with current approaches. This situation varies according to the patient's age, comorbidities, immunohistochemical subtype of the tumor, receptor status, and stage of the cancer.[2]

Many studies have been conducted to determine the factors affecting the prognosis and survival of breast cancer. It is also known that prognosis differs in young and elderly patients.[3] Young age is considered to be younger than 40 years, and it has been demonstrated that tumor biology and outcomes differ.[4]

Many factors have been found to affect breast cancer prognosis and survival. These factors include age, hormone receptors, histological subtype, molecular subgroup, grade, perineural invasion (PNI) status, lymphovascular invasion (LVI) status, Ki-67 percentage, lymph node metastasis, distant metastasis, tumor size, stage, and treatments applied to the patient.[5-7]

We know that prognostic factors and gene assay are effect the treathment of the breast cancer. In addition, studies on gene assay have shown that in older and younger patients

different genes have prognostic effectiveness.[8] In another study, it was determined that the survival results after recurrence of patients with close follow-up and the control group were different, and that close follow-up had an effect on survival.[9]

In this study, we aimed to analyze the prognostic factors and survival outcomes of breast cancer patients aged 40 years and older. We believe that these prognostic factors will be effective in the treatment and follow-up of the patient.

METHODS

The study was carried out with the permission of Ondokuz Mayıs University Clinical Researches Ethics Committee (Date: 31.12.2020, Decision No: 2020/717). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

A total of 1187 patients aged 40 years and older who were operated on at Ondokuz Mayıs University Department of General Surgery, between August 2005 and April 2019 and whose data were accessed were included. Patient information was obtained from the automation system, the online database of the Ministry of Health, the hospital archive, and patients and/or their relatives. Patients whose data could not be accessed were not included in the study.

Patients were classified separately according to the type of surgery performed, axillary metastasis status (according to radiological status if axilla surgery was not performed) (positive or negative), axilla surgery performed (sentinel lymph node biopsy or axillary lymph node dissection), pathological tumor size (pT0, pT1, pT2, pT3, pT4), pathological lymph node number (pN0, pN1, pN2, pN3), pathological stage (stage 0, stage 1, stage 2, stage 3, stage 4), pathological grade (grade1, grade 2, grade 3), lymphovascular and perineural invasion status (positive or negative), hormone receptor status (positive or negative), C-erb B2 status (positive or negative), Ki-67 percentage, histopathological types (ductal carcinoma in situ, invasive ductal carcinoma, invasive lobular carcinoma and others), and molecular subgroup (luminal A, luminal B, Her-2 positive, triple negative). Prognostic factors were analyzed both in terms of recurrence and mortality as well as survival analysis as univariate and multivariate analysis.

We used TNM staging. For hormone receptor status, even 1% positivity was accepted positive group. In immunohistochemical tests, C-erb b2 status was accepted negative if it is 0 or 1+ and positive if 3+. We used FISH results if it is 2+. In distinguishing molecular subgroups, we paid attention to C-erb B2 status and Ki-67 percentage to differentiate luminal A and luminal B. We accepted the Ki-67 cut-off value as 14% in our study.

Statistical Analysis

Statistical analyses were performed with IBM SPSS V22 (Chicago, USA). Categorical variables were compared with the chi-square test. Normality analysis of quantitative data was performed with the Kolmogorov-Smirnov test. The Ki-67 percentage did not follow a normal distribution and it was compared with the Mann-Whitney U test. It was accepted as the starting surgery date for the follow-up period. The first detected locoregional recurrence or distant metastasis was accepted the endpoint event for disease free survival (DFS). A new cancer in the contralateral breast after 5 years from first diagnosis is considered a different cancer. The death of the patient was accepted the endpoint event for survival. Survival analysis was performed with the Kaplan-Meier test. Variables with a significant effect on OS or DFS were identified in univariate analysis. Then, these variables were subjected to multivariate analysis using the cox regression test. Results were reported as independent prognostic factors. Data were presented as mean±standard deviation, n (%), and 95% confidence interval. Statistical significance was accepted as $p<0.05$.

RESULTS

Of the 1187 patients included in the study, 4 were male and 1183 were female. Histopathologic type, presence or absence of pathologic involvement of axillary lymph nodes, estrogen receptor (ER) positivity, progesterone receptor (PR) positivity, Her-2/neu status, PNI, LVI status, and Ki-67 percentage were statistically significant in terms of both recurrence and mortality (**Figure 1**, **Table 1**).

Patients were divided into three age groups: 40-69, 70-79, and 80 and above. There was no statistical difference between age groups in terms of recurrence, but a significant difference was observed in terms of mortality.

In the analysis in terms of molecular subgroup, there was no statistical difference between luminal A and luminal B in terms of recurrence and between the Her-2 positive group and triple negative group in terms of mortality, but a significant difference was observed between the other groups. The luminal A group had the lowest recurrence rate, and the luminal B group had the lowest mortality rate.

There was a statistically significant difference between the type of surgery, surgical intervention in the axilla, recurrence, and mortality. However, considering that the type of surgery was chosen according to the patient's stage, tumor size, whether the patient received neoadjuvant chemotherapy (NAC) or not, and patient preference, it was thought that it would be more appropriate to be determined by randomized controlled studies.

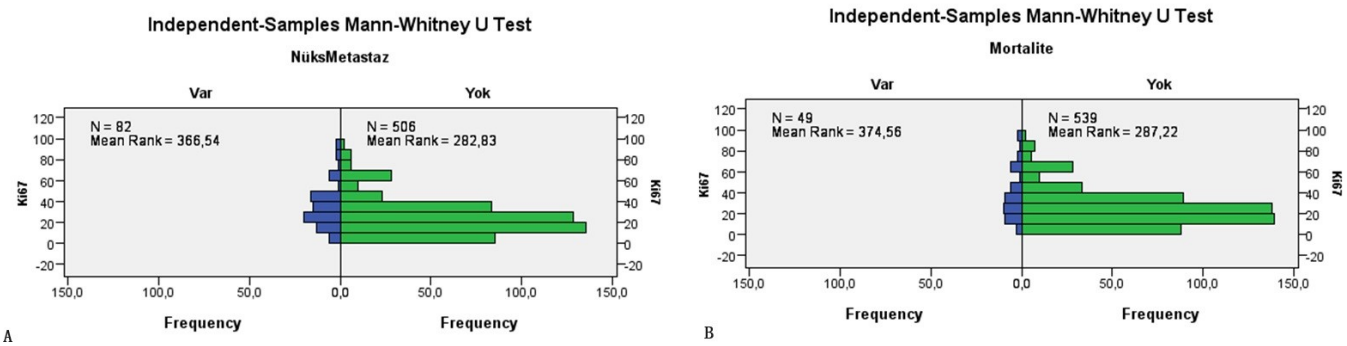

Figure 1. A-Comparison of Ki-67 and recurrence; B-Comparison of Ki-67 and mortality

Table 1. Comparison of individual variables in terms of recurrence and mortality

			Recurrence			Mortality		
			No	Yes	p	No	Yes	p
Histopathologic Type								
DCIS			58 (%96.7)	2 (%3.3)	<0.001	59 (98.3%)	1 (1.7%)	0.004
Invasive Ductal			759 (%79.3)	198 (%20.7)		780 (81.5%9)	177 (18.5%)	
Invasive Lobular			52 (%74.3%)	18 (%25.7)		58 (82.9%)	12 (17.1%)	
Others			90 (%90.0)	10 (%10.0)		88 (88.0%)	12 (12.0%)	
Pathologic axillary involvement								
Negative			547 (%88.8)	69 (%11.2)	<0.001	553 (%89.8)	63 (%10.2)	<0.001
Positive			362 (%71.3)	146 (%28.7)		384 (%75.6)	124 (%24.4)	
ER								
Negative			159 (%71.0)	65 (%29.0)	<0.001	162 (%72.3)	62 (%27.7)	<0.001
Positive			793 (%82.9)	164 (%17.1)		819 (%85.6)	138 (%14.4)	
PR								
Negative			258 (%72.5)	98 (%27.5)	<0.001	262 (%73.6)	94 (%26.4)	<0.001
Positive			692 (%84.1)	131 (%15.9)		717 (%87.1)	106 (%12.9)	
Her-2/neu								
Negative			637 (%82.4)	136 (%17.6)	0.005	654 (%84.6)	119 (%15.4)	0.015
Positive			258 (%75.4)	93 (%24.6)		298 (%78.8)	80 (%21.2)	
PNI								
Negative			624 (%84.0)	119 (%16.0)	<0.001	637 (%85.7)	106 (%14.3)	0.012
Positive			135 (%71.4)	54 (%28.6)		148 (%78.3)	41 (%21.7)	
LVI								
Negative			541 (%87.4)	78 (%12.6)	<0.001	552 (%89.2)	67 (%10.8)	<0.001
Positive			266 (%69.5)	117 (%30.5)		281 (%73.4)	102 (%26.6)	
Age group								
40-69			852 (%80.1)	212 (%19.9)	0.259	900 (%84.6)	164 (%15.4)	<0.001
70-79			84 (%85.7)	14 (%14.3)		70 (%71.4)	28 (%28.6)	
80+			22 (%88)	3 (%12)		15 (%60)	10 (%40)	
Molecular Subgroup								
Luminal A			400 (84.0%)	76 (16.0%)	<0.001	401 (84.2%)	75 (15.8%)	<0.001
Luminal B			386 (80.4%)	94 (19.6%)		410 (85.4%)	70 (14.6%)	
Her-2 +			77 (70.6%)	32 (29.4%)		81 (84.3%)	28 (25.7%)	
Triple neg.			61 (70.1%)	26 (29.9%)		61 (70.1%)	26 (29.9%)	
Types of axilla operation								
SLNB			639 (88%)	87 (12%)	<0.001	656 (90.4%)	70 (9.6%)	<0.001
ALND			269 (68.3%)	125 (31.7%)		278 (70.6%)	116 (29.4%)	
SLNB		Pat. LAP			0.009			
		Negative	506 (%89.7)	58 (%10.3)		517 (%91.7)	47 (%8.3)	
		Pat. LAP						0.026
		Positive	133 (%82.1)	29 (%17.9)		139 (%85.8)	23 (%14.2)	
ALND		Pat. LAP			0.063			
		Negative	39 (%79.6)	10 (%20.4)		33 (%67.3)	16 (%32.7)	
		Pat. LAP						0.598
		Positive	229 (%66.4)	116 (%33.6)		245 (%71)	100 (%29)	
SLNB		NAC			<0.001			
		Negative	561 (%91.5)	52 (%8.5)		558 (%91)	55 (%9)	
		NAC						0.155
		Positive	78 (%69)	35 (%31)		98 (%86.7)	15 (%13.3)	
ALND		NAC			<0.001			
		Negative	229 (%72.5)	87 (%27.5)		233 (%73.7)	83 (%26.3)	
		NAC						0.005
		Positive	39 (%50)	39 (%50)		45 (%57.7)	33 (%42.3)	
Grade								
	Grade1		93 (%94.9)	5 (%5.1)		88 (%89.8)	10 (%10.2)	
	Grade2		502 (%81.4)	115 (%18.6)	<0.001	513 (%83.1)	104 (%16.9)	0.148
	Grade3		346 (%76.5)	106 (%23.5)		369 (%81.6)	83 (%18.4)	
Pathological tumor size								
T0			88 (%87.1)	13 (%12.9)		94 (93.1%)	7 (6.9%)	
T1			390 (%86.3)	62 (%13.7)		401 (88.7%)	51 (11.3%)	
T2			415 (%81.1)	97 (%18.9)	<0.001	418 (81.6%)	94 (18.4%)	<0.001
T3			48 (%57.1)	36 (%42.9)		51 (60.7%)	33 (39.3%)	
T4			16 (%43.2)	21 (%56.8)		20 (54.1%)	17 (45.9%)	
T0		Pat. LAP						
		Negative	59 (%88.1)	8 (%11.9)		62 (%92.5)	5 (%7.5)	
T1		Pat. LAP						
		Negative	265 (%89.8)	30 (%10.2)		270 (%91.5)	25 (%8.5)	
T2		Pat. LAP			0.494			0.006
		Negative	202 (%88.2)	27 (%11.8)		203 (%88.6)	26 (%11.4)	
T3		Pat. LAP						
		Negative	202 (%88.2)	27 (%11.8)		203 (%88.6)	26 (%11.4)	
T4		Pat. LAP						
		Negative	17 (%89.5)	2 (%10.5)		15 (%78.9)	4 (%21.1)	
Number of removed lymph nodes								
SLNB			637 (%88.1)	86 (%11.9)	<0.001	653 (%90.3)	70 (%9.7)	
ALND<10			133 (%72.7)	50 (%27.3)		141 (%77)	42 (%23)	<0.001
ALND>10			139 (%63.8)	79 (%36.2)		143 (%65.6)	75 (%34.4)	
pN								
N0			553 (%88.8)	70 (%11.2)		559 (%89.7)	64 (%10.3)	<0.001
N1			268 (%80)	67 (%20)		273 (%81.5)	62 (%18.5)	
N2			71 (%61.7)	44 (%38.3)	<0.001	82 (%71.3)	33 (%28.7)	
N3			23 (%40.4)	34 (%59.6)		29 (%50.9)	28 (%49.1)	
Stage								
Stage 0			81 (%95.3)	4 (%4.7)		83 (%97.6)	2 (%2.4)	
Stage 1			279 (%91.2)	27 (%8.8)		284 (%92.8)	22 (%7.2)	
Stage 2			482 (%87.5)	69 (%12.5)	<0.001	472 (%85.7)	79 (%14.3)	<0.001
Stage 3			116 (%60.7)	75 (%39.3)		131 (%68.6)	60 (%31.4)	
Stage 4			0 (%0)	54 (%100)		15 (%27.8)	39 (%72.2)	

Patients who underwent sentinel lymph node biopsy (SLNB) and axillary lymph node dissection (ALND) were analyzed separately according to the presence or absence of pathologic involvement. While there was a statistical difference in both recurrence and mortality in patients who underwent SLNB, no significant difference was observed in patients who underwent ALND. Again, patients who underwent SLNB and ALND were analyzed according to whether they received NAC or not. In both groups, a statistical difference was observed in terms of recurrence after receiving NAC, while a significant difference was observed in terms of mortality only in patients who underwent ALND.

There was a significant difference between grade and recurrence, but no significant difference between grade and mortality.

In the comparison between pathological tumor size and recurrence, pT0, pT1, and pT2 were similar among themselves; pT3, and pT4 were similar among themselves; in terms of mortality, pT0, pT1, pT3, and pT4 were similar among themselves, while there was a statistical difference between the other groups. When patients without axillary metastasis were re-examined in terms of pathological tumor size, a statistical difference was observed between pT4 and the others only in terms of mortality.

In the analysis, according to the number of lymph nodes dissected from the axilla, the groups with less than 10 lymph nodes and more than 10 lymph nodes were similar in terms of recurrence, while a significant difference was observed between these groups with SLNB. In terms of mortality, there was a difference between all groups. According to the number of lymph nodes with pathologic involvement, there was a significant difference between all groups in terms of recurrence. In terms of mortality, pN1 and pN2, pN2 and pN3, were similar, while a significant difference was observed between the other groups.

Table 1. Comparison of variables in terms of 5-year survival and disease-free survival

	5-year survival			5-year disease-free survival		
	Rate	Average duration (month)	p	Rate	Average duration (month)	p
Total patients	%88.8	55.9		%83.4	52.6	
Histopathologic type						
DCIS	%100		p=0.011	%96.7	59.7	
Invasive Ductal	%87.9	55.6		%81.6	51.7	
Invasive Lobular	%85.7	54.3		%84.3	53.0	p=0.002
Others	%93	57.9		%92	56.6	
Pathologic axillary involvement						
Negative	%94.6	58.1	p<0.001	%90.3	56.1	p<0.001
Positive	%82.7	54.0		%75.8	49.1	
ER						
Negative	%78.6	51.7	p<0.001	%72.3	47.6	p<0.001
Positive	%91.1	56.9		%85.9	53.8	
PR						
Negative	%80.9	53.0	p<0.001	%74.2	48.8	p<0.001
Positive	%92.1	57.2		%87.2	54.2	
Her-2/neu						
Negative	%89.7	56.1	p=0.138	%85.1	53.1	p=0.007
Positive	%86.2	55.3		%78.3	50.9	
PNI						
Negative	%89.8	56.0	p=0.238	%85.7	53.7	p=0.003
Positive	%85.7	56.0		%76.7	49.0	
LVI						
Negative	%92.6	57.2	p<0.001	%89	55.0	p<0.001
Positive	%82.5	54.0		%74.4	48.7	
Molecular Subgroup						
Luminal A	%91.2	56.9	p<0.001	%88.2	54.6	p<0.001
Luminal B	%89.6	56.2		%82.1	52.1	
Her-2 +	%82.6	53.7		%72.5	48.3	
Triple negative	%75.9	50.2		%71.3	46.5	
Grade						
Grade1	%94.9	59.0	p=0.009	%95.9	57.9	
Grade2	%89.6	56.3		%84.9	53.5	p<0.001
Grade3	%86.3	54.7		%78.1	49.9	
Pathological tumor size						
T0	%95	57.7	p<0.001	%87.1	54.6	
T1	%92.5	57.4		%88.1	54.7	
T2	%89.8	56.5		%84.2	53.2	p<0.001
T3	%67.9	47.9		%61.9	42.2	
T4	%59.5	45.5		%54.1	36.0	
pN						
N0	%94.5	58.0	p<0.001	%90.2	56.1	p<0.001
N1	%87.5	55.1		%82.4	51.5	
N2	%77.4	53.4		%67.8	45.7	
N3	%66.7	50.0		%54.4	42.8	
Stage						
Stage 0	%98.8	59.5	p<0.001	%95.3	58.6	
Stage 1	%95.8	58.6		%92.8	57.2	
Stage 2	%92.6	57.3		%89.7	56.0	p<0.001
Stage 3	%77	52.9		%68.1	47.7	
Stage 4	%37	33.9		%1.9	0.0	

In terms of stage, stages 0, 1, and 2 were similar in terms of recurrence, and stages 1 and 2 were similar in terms of mortality, while a significant difference was observed between the other groups.

The 5-year disease-free survival rate was 88.8% and the mean survival time was 55.9 months, while the 5-year disease-free survival rate was 83.4% and the mean disease-free survival time was 52.6 months. In individual analyses, PNI and Her-2 neu status were statistically significant only in terms of disease-free survival, while LVI, ER, PR positivity, Ki-67 percentage, grade, tumor diameter, lymph node involvement and number of involved lymph nodes, stage, molecular subgroup, and histological type were statistically significant in terms of both survival and disease-free survival. In the multivariate analysis, excluding the type of surgery and NAC status, which disrupted the homogeneous distribution, PNI, LVI, grade, and PR positivity were found to be independent factors for recurrence, while LVI and PR positivity were found to be independent factors for mortality (**Table 2**).

DISCUSSION

Since breast cancer is the most common cancer in women, it has been of great importance, and much research has been done on it in the world and in Turkey. In history, it started with catastrophic surgeries such as radical mastectomy, and with the discovery and development of treatments such as chemotherapy, radiotherapy, and hormone therapy, more moderate surgeries were performed. Today, oncoplastic surgery and protocols with very good aesthetic results are applied to appropriate patients.

It has been and continues to be investigated which treatment will be more beneficial for patients, the expected recurrence and mortality rates in the future, and which treatments can minimize them. In this respect, prognostic factors gain importance. In addition, some of the prognostic factors are also important in terms of directing the treatment choices of patients.[10,11]

Many models have been established for prognostic factors determining mortality and recurrence.[12,13] Phung et al.[13] conducted a study examining these models and found that the most commonly used predictors in these models were tumor size, nodal involvement, age, grade, and ER status. In our study, these factors were found to be statistically significant, and grade was found to be an independent factor in terms of recurrence.

In the Makower et al.[14] study, factors associated with poor survival were found to be LVI, axillary involvement, tumor size, grade, and comorbid diseases, and LVI was found to be a prognostic marker in N0 patients. In a cohort study conducted in China, tumor size, grade, LVI, number of metastatic lymph nodes, and hormone receptor status were found to be associated with both survival and disease-free survival, whereas age, distant metastasis, and Ki-67 percentage were only associated with survival.[15] In other studies, LVI was found to be an independent prognostic factor for survival and disease-free survival in early breast cancer.[16-18] In our study, LVI was found to be an independent prognostic factor for both recurrence and mortality.

PR is an important receptor involved in both normal mammary gland development and breast carcinogenesis.[19] PR also plays an important role in determining the molecular subtype of breast cancer and in the effectiveness of hormonotherapy.[20] PR positivity has been reported to affect the response to hormone therapy and therefore has a prognostic effect.[21] A meta-analysis revealed that ER and PR loss were significantly associated with prognosis in terms of survival and survival after recurrence.[22]

Perineural invasion was found to be an independent prognostic factor in our study, as in the study by Hosoya et al.[23] In another study, multivariate analysis of prognostic factors revealed a significant association between PNI and locoregional recurrence.[24]

Study Limitations

Although the count of patients is high, the patient distribution is not homogeneous. Therefore, the possibility of prognostic factors being affected by each other increases. Although independent factors are identified by performing multivariate analyses, we think that analyzes on more homogeneously distributed patient groups or prospective studies will provide better information.

CONCLUSION

In this study, PNI, LVI, grade, and PR status were found to be independent prognostic factors for recurrence, while LVI and PR status were found to be independent prognostic factors for mortality. We think that regulating follow-up and treatment by taking these factors into consideration will improve survival and disease-free survival. In addition, it will allow us to make predictions in terms of close follow-up of patients, thus indirectly affecting survival.

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ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ondokuz Mayıs University Clinical Researches Ethics Committee (Date: 31.12.2020, Decision No: 2020/717).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Developmental anomalies of the breast in the pediatric population

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ABSTRACT

Pediatric breast conditions, which rarely require biopsy or excision and where follow-up with ultrasound is sufficient, are usually temporary. To understand childhood's physiological and pathological conditions, it is necessary to know the stages of intrauterine development, as in every organ. In neonatal and subsequent childhood periods, ultrasound is sufficient as a radiological examination after history and physical examination. Malign masses are sporadic, and benign masses are rarely encountered. Parental anxiety is an essential factor affecting patient management from the first admission to the final follow-up examination. For this reason, practitioners need to know information that reassures patients and parents with an appropriate methodology in developmental breast diseases.

Keywords: Children, breast, developmental anomalies

INTRODUCTION

From the fifth week in the embryological period, the milk streak (mammary ridge) develops bilaterally in the ectodermal layer along the trunk from the axilla to the groin. Although many paired mammary glands develop along this ridge, they disappear shortly after formation, except for a portion in the anterior fourth intercostal space. Until birth, solid epithelial columns comprising 15-20 branches with specialized epithelium canalize to form lactiferous ducts. The ducts continue to form lobules, which continue until the formation of a solid dermal button that will form the nipple between 7 and 12 weeks intrauterine week. Mesenchyme, which will become the connective and fatty tissue supporting the breast, surrounds the epithelial system. Although there is a temporary pit during the epithelial invagination of the nipple from the skin, close to birth, this pit extends outwards and forms the nipple. If there is a disruption at this stage, inverted nipples will rarely occur at birth. The breast consists of lactiferous ducts without alveoli from birth to puberty. Breast development has the same developmental stages in both genders until puberty. During the pubertal period under hormonal influences, the ducts that will form the breast lobules in the future begin to proliferate, and their terminations form solid masses of cells.[1-3]

The thelarche period, when breast development begins in girls at the age of 9-10, represents the beginning of the puberty period. In thelarche, which starts with the completion of the terminal duct lobular unit in the breast, estrogen triggers ductal growth, and progesterone triggers lobular and alveolar differentiation.[4,5]

This stage of breast development concerns the pubertal period, which is the beginning of the first step into adulthood. There are no breast problems that would put the clinician in a problematic situation. For example, thelarche that begins at 7-8 is called the premature thelarche and is seen in prepubertal girls. Thelarche, the beginning of secondary breast development, is considered delayed if it begins after twelve years old. In such a case, if there is no source of hormonal pathology originating from the ovary or adrenal gland, the patient can be followed up by an endocrinologist after this stage.

In the pediatric population, except for developmental breast changes from the neonatal period to adolescence, benign masses occur at rates as low as 3%, especially after puberty. Malignant breast diseases are encountered sporadically at a rate of 1/100000. This study will discuss developmental childhood breast conditions other than rare benign and malignant diseases.

1. DEVELOPMENTAL ANOMALIES OF THE BREAST

1.1. Polythelia

In the fetus, after the 12th intrauterine week, a residue in the mammary ridge from the axilla to the groin, other than the usual location, causes polythelia (supernumerary nipples). The most common location is just below the breast or on the skin of the abdomen. Incidence is 0.2 to 2.5 percent. This abnormality, seen bilaterally in fifty percent, has been reported to be rarely seen, even in the scapula, head, neck, and thighs. While there is no diagnostic or symptomatic problem with this anomaly, clinicians should remember that it may accompany urological malformation or malignancy.[6-8]

1.2. Ectopic Breast Tissue

Ectopic breast tissue, in embryological life, occurs from the residue outside the original breast location, where the mammary ridge is located, as in polythelia. The presence of ectopic or accessory breast is called polymastia. Ectopic breast tissue may contain components of the mammary gland, including the nipple, areola, and glandular tissue, and may be exposed to benign and malignant breast diseases. Ectopic breast, which has a prevalence of 2-6 percent in the literature, constituted 3.2% of our breast patients (17 out of 409) in the last eight years. If ectopic breast tissue is usually in the axillary region and cannot be diagnosed with ultrasound, fine needle aspiration biopsy can be performed. Total excision should be performed if these patients have aesthetic concerns and suspicion of benign or malignant disease.[7,9]

1.3. Premature Thelarche

It is an annoying condition in girls under 7.5 years of age, where there is only premature breast growth in the absence of secondary sex characteristics (such as pubic hair, menarche, and axillary hair growth). Regular follow-up is sufficient unless the patient has pelvic ultrasound and biochemical hormone findings indicating precocious puberty.[4,10]

1.4. Neonatal Breast Hypertrophy

Although it is accepted in the literature that maternal estrogen is the etiological factor of breast hypertrophy seen in newborns, it has been understood that placental-derived estrogen causes this condition. This is because there is no direct hormone transfer from mother to fetus in intrauterine life. Breast hypertrophy, which is generally seen in seventy percent of newborns, is more common in females, and galactorrhea may be observed in 5% of patients. This situation (galactorrhea) is popularly known as witch's milk. Although ultrasound is performed on such babies due to the family's concern, the finding on the ultrasound indicates that there are only secretory ducts and no lobules, so no negative situation is encountered. In short, hypertrophy, which becomes evident in the first week of life, is temporary.[2,5,9,11]

1.5. Hemangioma and Lymphangioma

Pre-adolescent breast hypertrophy may be accompanied by hemangioma and lymphangioma. Even if it is recognized by clinical appearance, the diagnosis can be confirmed with ultrasound and magnetic resonance. Hemangioma and lymphangioma treatment protocols vary from case to case.[1]

1.6. Mammary Duct Ectasia in Infantile

This entity, whose etiology is unknown, has been tried to be demonstrated by the presence of large dilated mammary ducts in postmortem studies in healthy one-three-year-old children. Bloody discharge from the nipple is the most common symptom and palpable mass may accompany it. While this disease shows symptoms at this age with mini-puberty symptoms, it may be seconder to inflammation, bleeding, and duct obstruction in the breast in older children. It is more common in the male child population. This disease is temporary, requiring appropriate conservative treatment, and a process that follows with parental reassurance usually suffices.[1,2,12]

1.7. Nipple Inversion in Newborn

Its overall prevalence is approximately two percent. This anomaly is caused by the breast ducts remaining shorter than usual during the fetal period and being inverted into the areola with fibrous bands. When such baby girls reach adulthood, they do not experience breastfeeding difficulties due to changes in the breast during pregnancy. Still, this anomaly may need to be corrected with a mini operation.[1,3,13]

1.8. Lipomastia

It occurs in obese children due to the increase in fat tissue in the breast. If it cannot be differentiated from gynecomastia during physical examination, a differential diagnosis can be made with ultrasound. The absence of glandular tissue under the areola when the patient is in a sitting position is a helpful factor in diagnosis.[4]

1.9. Gynecomastia

Among the robust assumptions that familial factors are influential, Gynecomastia is seen in 4-64% between the ages of 10-13, typically six months after the emergence of secondary sex characteristics. Although this condition disappears around the age of 17, it is a benign process and regresses on average in two years. The etiology of this pathology, which is especially seen in prepubertal boys, cannot always be determined. Exposure to endogenous or exogenous estrogen is the most considered etiological factor. The main ones that should be investigated as endogenous sources are gonadal or adrenal tumors, gonadotropin-secreting tumors such as hepatocellular carcinoma or choriocarcinoma, aromatization of androgens associated with Sertoli cell and sex cord testicular tumors, and Klinefelter syndrome. Estrogenic and antiandrogenic effects of cosmetic products as exogenous sources may carry out gynecomastia.[14] Recently, it has been stated that Leptin, which is found in breast epithelial cells and causes an increase in estrogen concentration by increasing aromatase enzyme activity in adipose tissue and breast tissue, may be effective in the etiology of gynecomastia.[15] Treatment is often not required unless gynecomastia is persistent and severe.[14,15]

1.10. Asymmetrical Breast Development and Related Diseases During Adolescence

Although breast asymmetry develops from infancy to adolescence, emotional pathology may occur in adolescents as self-esteem becomes dominant in adolescence. In this case, although gynecomastia in male adolescents is diagnosed through clinical examination, ultrasound can be performed for the reassure of the family and the patient. If the clinician has suspicious examination findings in marked asymmetry,

extreme diseases such as fibroadenoma should be considered with ultrasound and other examinations. Apart from breast asymmetry and physiological asymmetry in girls with scoliosis, true breast asymmetry may be congenital in cases of amastia, hypomastia, and Poland syndrome.[16-18]

Amastia, which is usually accompanied by other embryological ectodermal defects and where the ridge of the breast does not develop or is completely involuted, also accompanies Poland syndrome. Amastia or hypomastia may be seen in Poland syndrome, which is characterized by the complete absence of unilateral chest wall muscles and ipsilateral rib cage and upper limb defects. Surgical procedures to correct breast asymmetry in adolescents should be postponed until breast development is completed.[16-19]

1.11. Adolescent Breast Hypertrophy

This entity, also known as juvenile or virginal breast hypertrophy, refers to sudden and progressive breast growth over a few months. Since it contains histological findings of gynecomastia, it is also called gynecomastoid breast hypertrophy. Antiestrogenic drugs such as tamoxifen are used to stop breast growth in this hypertrophy, which can also be familial and cause embarrassment and back pain in girls. Even if breast growth is partially halted, this situation needs to be corrected with surgery.[17,20]

1.12. Fibrocystic Changes in The Breast

This condition, which was known as "fibrocystic disease" until the nineties, is the manifestation of macroscopic and microscopic cysts, apocrine metaplasia, fibrosis, and duct adenosis in the breast, resulting from the imbalance between estrogen and progesterone, and accompanying epithelial hyperplasia in its histopathology.

Especially during pre-menstrual periods, breast tenderness and orange peel-like nodularity are palpable on examination. There are no specific findings on ultrasound other than cysts and fibrosis areas. The patient is followed at regular intervals.[17,21]

CONCLUSION

In the pediatric population, healthcare providers to whom breast patients consult from the neonatal period to the age of 18 should be knowledgeable about developmental physiological and pathological breast conditions. Because parents experience intense anxiety, thinking that their child may develop breast cancer similar to that seen in adults.[22] Pediatric breast conditions, which rarely require biopsy or excision and where follow-up with ultrasound is sufficient, are usually temporary.

ETHICAL DECLARATIONS

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Journal of Comprehensive Surgery

Case Report

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Intestinal obstruction delaying the diagnosis of acute appendicitis: a case presentation

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ABSTRACT

Acute appendicitis is the most common surgical emergency worldwide. Patients often present with symptoms such as abdominal pain, migrating pain, loss of appetite, nausea, and vomiting. Signs of intestinal obstruction are rarely detected in patients. A 55-year-old male patient presented to the emergency department with complaints of abdominal distension, nausea, and vomiting, leading to admission to the surgical clinic with a diagnosis of intestinal obstruction. Due to the predominance of obstruction symptoms in the patient and the inadequacy of radiological evaluations due to the dilatation of bowel loops, emergency surgery was not performed. Following monitoring in the ward, laparotomy was performed in the patient, revealing a complete obstruction at 90 cm from the ileocecal valve, and a diagnosis of acute appendicitis was established. Appendectomy was performed, and the patient was discharged in a healed condition. Acute appendicitis can rarely lead to intestinal obstruction and may present with unexpected clinical manifestations.

Keywords: Acute appendicitis, intestinal obstruction, small bowel

INTRODUCTION

Mechanical obstructions are the most common surgical pathologies affecting the small intestine. Intestinal obstruction is defined as the partial or complete blockage of the passage of contents from proximal to distal.[1] Although adhesions resulting from prior surgeries are the most common cause, malignancies, volvulus, and Crohn's disease occasionally contribute to the etiology. When obstructions become complicated with strangulation, mortality can reach up to 30%.[2]

Acute appendicitis is most frequently characterized by abdominal pain, loss of appetite, nausea, and vomiting, making it the leading cause of emergency room visits. Among etiologies causing abdominal pain, acute appendicitis is the most common reason for acute abdomen.[3] Delayed cases may present with complications such as perforation, peritonitis, or obstruction. Adhesions developed secondary to inflammation or complication-related perforation of the appendix can lead to obstruction, given the appendix's mobile nature, allowing obstructions and adhesions to develop in a different area than the primary site.

Our presented case report delineates the surgical intervention and subsequent monitoring of a 55-year-old patient within our clinic. The primary objective was to articulate the potential of acute appendicitis to induce an ileus scenario even in the absence of perforation. We aimed to underscore the necessity of contemplating acute appendicitis in conjunction with adhesions, arising from previous surgeries, to foster a comprehensive clinical understanding.

CASE

A 55-year-old patient with no known medical history presents to the emergency department with isolated abdominal pain. The patient, for whom surgical consultation was not sought, is discharged from the emergency department after symptomatic treatment. On the 4th day of symptoms, the patient returns to the emergency department with the development of nausea and vomiting, prompting a general surgery consultation.

The patient was evaluated in the emergency department. On physical examination, the abdomen is soft, with no signs of rebound tenderness or defense, and minimal distension is present. A previous open cholecystectomy procedure has left a right subcostal incision. Complete blood count reveals no leukocytosis, with a white blood cell count of 4.8x103/mm^3, and other parameters are within normal limits. The patient is afebrile, and vital signs are stable. Nausea, which started 2 hours after eating, is reported.

Direct abdominal X-ray shows the presence of air-fluid levels (**Figure 1**). No irreducible hernia is detected. The contrast-enhanced abdominal tomography is interpreted as "no evidence in favor of acute appendicitis; prominent dilatation of bowel loops and air-fluid levels consistent with ileus".

Considering the possibility of obstruction due to adhesions, the patient was admitted to the surgical ward and monitored with oral closed nasogastric decompression. At the 36th hour of admission, an increase in distension and the detection of acute abdominal signs led to the decision to perform emergency laparotomy (**Figure 2**).

Extensive dilation of the small intestines was observed, with adhesions accompanied by an inflamed appendix causing complete obstruction at 90 cm from the ileocecal valve (**Figure 4**). The adherent area was dissected, and an appendectomy was performed (**Figure 3**). The area causing the obstruction and other bowel loops appeared normal.

The patient's oral intake was closely monitored in the postoperative surgical service. The nasogastric drainage tube was removed on postoperative day 24, and oral intake was initiated. The patient, who tolerated oral intake, was discharged on the second postoperative day with nutritional recommendations.

Figure 1. First hospitalization x-ray

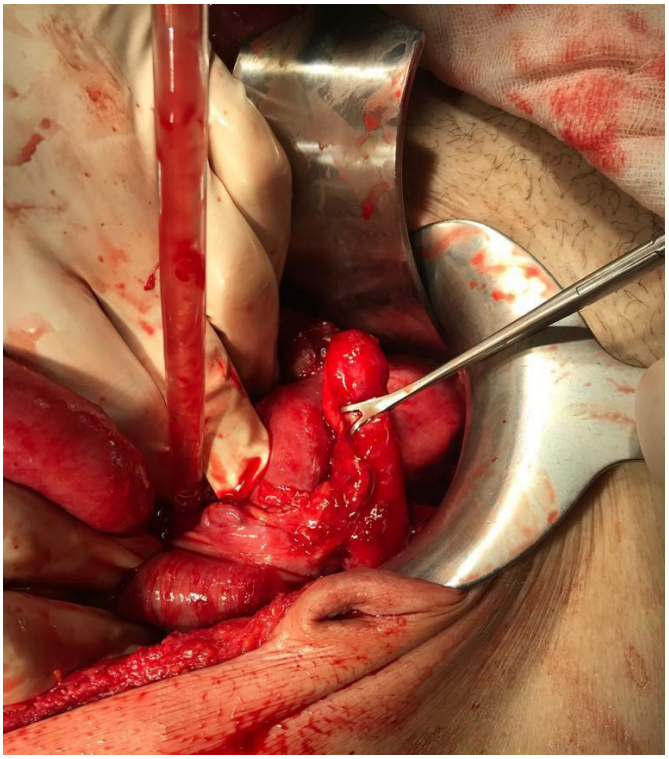

Figure 3. Inflamed appendix

Figure 2. Pre-op x-ray

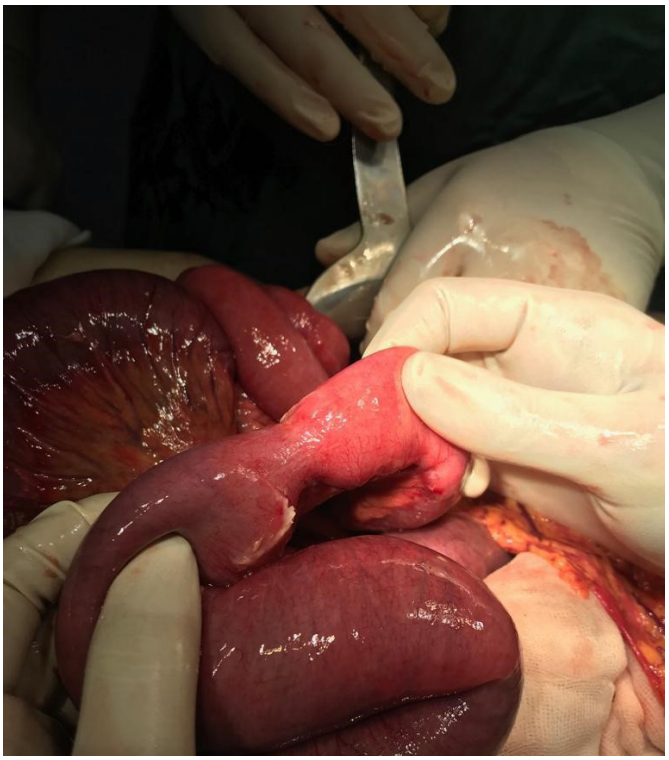

Figure 4. Obstructed area of small intestine

DISCUSSION

Acute appendicitis is the most common etiology requiring surgical intervention in cases of acute abdomen. Physical examination and a thorough anamnesis are often sufficient for diagnosis. Laboratory tests indicating leukocytosis and imaging findings consistent with acute appendicitis further support the diagnosis. In the present era, complete treatment is achievable through both laparoscopic and open surgical approaches. On the other hand, small bowel obstructions are also frequent reasons for hospital admissions, constituting 15% of cases requiring emergency surgery.[4] Postoperative adhesions account for 60% of the causes of intestinal obstructions. Investigating the etiology of acute abdomen demands careful attention, as intra-abdominal pathologies may present with unusual symptoms. Rare causes of small bowel obstructions include bezoars, B-cell lymphoma, foreign bodies, gallstones, and endometriosis.[5]

Mechanical obstruction due to acute appendicitis is a seldom-seen phenomenon. While investigating the etiology of acute abdominal conditions in a patient, the prominence of symptoms and signs of intestinal obstruction, a history of previous abdominal surgery, can mask the actual cause of acute abdomen. This situation may lead to the progression of the primary pathology with complications. Harris and colleagues, in 1966, first reported cases where acute appendicitis presented with signs of obstruction, most of which revealed perforation and secondary adhesions. However, in some cases, the cause of obstruction was the displacement of the omentum to the right iliac fossa, leading to the bending of the small intestine.[6] In our case, no perforation was observed in the appendix, and it was noted that the inflamed appendix tissue had shifted to the right iliac fossa along with a small segment of the small intestine.

CONCLUSION

The patient's history of previous abdominal surgery, the presence of obvious air-fluid levels at the time of admission, the computed tomography (CT) scan only mentioning air-fluid levels without a clear diagnosis of appendicitis, the absence of rebound tenderness and leukocytosis in the lower right quadrant guided us towards a diagnosis of postoperative adhesion-related obstruction. Although the detection rate of acute appendicitis on CT scans reaches up to 93%, this condition may be overlooked by radiologists. In conclusion, acute appendicitis can lead to mechanical obstruction, and the resultant intestinal dilation may mask both clinical and radiological findings.

ETHICAL DECLARATIONS

Informed Consent: All patients signed the free and informed consent form.

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Case Report

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A rare case of acute abdomen: acute appendicitis in a patient with midgut malrotation

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ABSTRACT

Acute appendicitis (AA) is the most common pathology requiring surgery in patients presenting to the emergency department with abdominal pain. AA is usually suspected and diagnosed with abdominal pain localized to the right lower quadrant based on anamnesis and physical examination findings. Atypical anatomical localizations of the appendix vermiformis often do not give typical anamnesis and examination findings and cause delays in diagnosis and treatment. In the presence of Midgut Malrotation (MM) and Situs Inversus Totalis (SIT), the appendix is localized in the left lower quadrant due to malrotation. In this article, we report a case of non-rotation type Midgut Malrotation that presented with left lower quadrant pain and was diagnosed with acute appendicitis.

Keywords: Appendicitis, malrotation, abdominal pain

INTRODUCTION

Abdominal pain is one of the most common complaints in emergency room visits. The most common pathology requiring surgery in these patients is acute appendicitis (AA).[1] It is seen in the general population at a rate of 0.1% per year.[2] Patients usually have typical anamnesis and physical examination findings localized to the right lower quadrant. This is due to the normal anatomical position of the appendix vermiformis in the right lower quadrant, and these findings vary according to the localization.[3] Midgut malrotation (MM) is a rare fetal anomaly caused by incomplete or failed midgut rotation and fixation.[4] The diagnosis of AA is difficult and delayed in patients with MM because of the left lower quadrant location of the appendix.[5] In this article, we report a patient who presented with left lower quadrant pain, was found to have non-rotation type Midgut Malrotation , and was diagnosed with acute appendicitis.

CASE

A 32-year-old woman with no comorbidities other than hypothyroidism and a history of previous cesarean delivery was admitted to the emergency department of an external center with the complaint of abdominal pain that started 2 days ago, accompanied by anorexia, nausea, and vomiting, localized in the left lower quadrant of the epigastrium. He was referred to our hospital after blood tests and abdominal computed tomography (CT) performed at an external center revealed an appearance compatible with MM and AA. A physical examination at the time of admission to the emergency department revealed marked tenderness, defense, and rebound in the left lower quadrant. Blood tests revealed leukocytosis (19.00x10^9/L), no abnormality in biochemical parameters, and a C-reactive protein value of 12.1 mg/L.

A chest radiograph taken in the emergency department showed that the heart was located on the left and the gastric fundus gas was on the left (**Figure 1**). External center tomography interpretation was obtained by the radiology team of the emergency department of our hospital, and it was reported as liver, stomach, spleen in normal position and size, cecum in the midline (malrotation?) and compatible with AA (diameter 17.1 mm, periapendicular fatty tissue dirty, and wall edematous) (**Figure 2-3**).

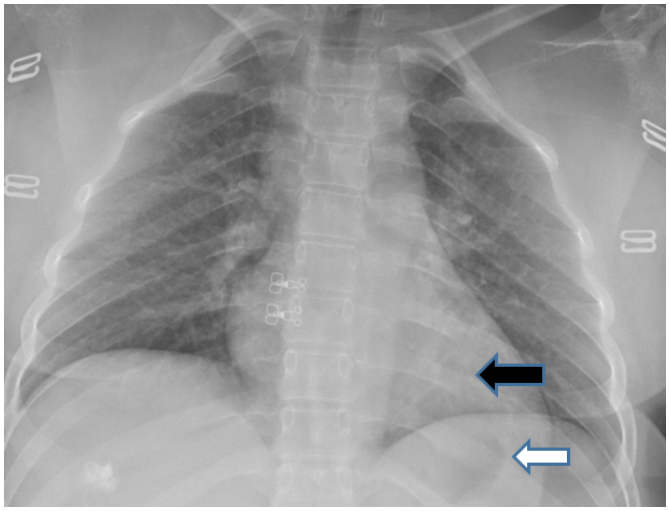

Figure 1. The chest X-ray shows a left-sided heart (black arrow) and gastric fundus gas (white arrow)

Figure 2. Computed tomography shows a left-sided appendix with periapendicular contamination and a wall thickness of 17.1 mm

Figure 3. Computed tomography shows the cecum and ascending colon located in the left quadrant of the abdomen

As a result of the investigations and physical examination, the patient was diagnosed with AA and hospitalized for surgery. Considering the possibility of anatomical variation, a laparoscopic appendectomy was decided. On laparoscopic exploration, contrary to normal anatomy, jejunum and ileum was located in the right lower quadrant, the terminal ileum entered the cecum from the right, the cecum and total colon were located in the left quadrant, and the appendix was inflamed-erectile and edematous in the left lower quadrant (**Figure 4-5**). The appendectomy was successfully completed laparoscopically (**Figure 4**). No complications were observed in the postoperative period, and the patient was discharged on the 1st postoperative day with healing.

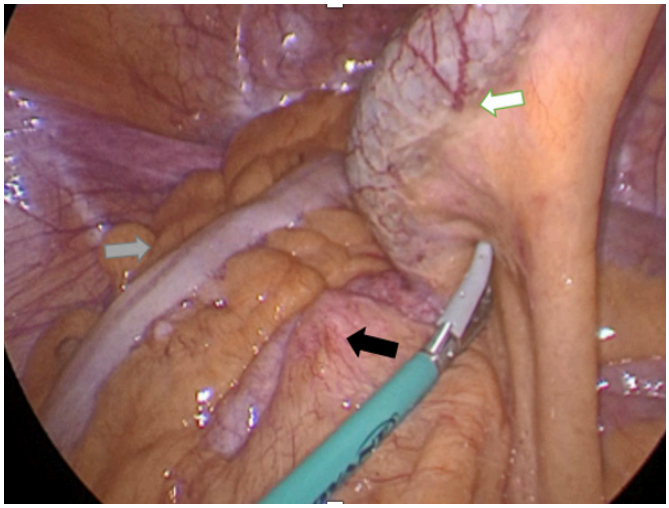

Figure 4. Inflamed-erectile appendicitis with increased vascularity (white arrow) and a left-sided cecum (black arrow) juxtaposed with a sigmoid colon (gray arrow) is shown on laparoscopic exploration

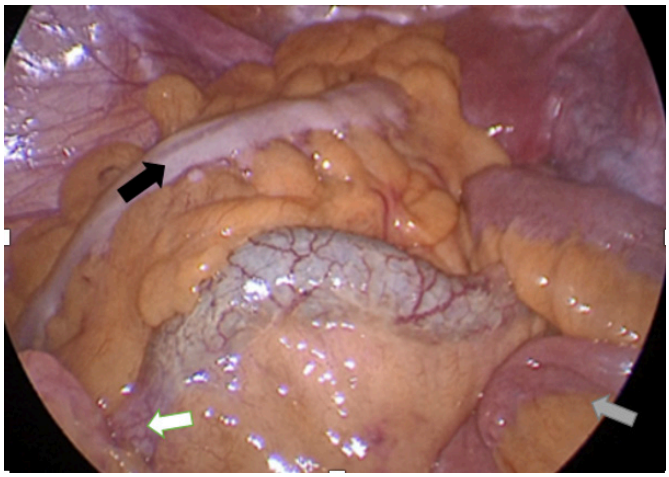

Figure 5. Laparoscopic exploration shows the appendix stump (white arrow) and right ileal anus (gray arrow) adjacent to the sigmoid colon (black arrow)

DISCUSSION

AA is an acute inflammation of the appendix vermiformis, which is the most common abdominal surgical pathology in the world.[6] It is typically recognized with pain that starts as a feeling of discomfort around the umbilicus, accompanied by symptoms such as nausea, fever, and anorexia, and localizes to the right lower quadrant as the inflammation increases. However, findings may vary due to positional variations in the appendix. In retrocaecal, subhepatic, pelvic, subcaecal, preileal, and postileal appendicitis, pain and examination findings may shift to other quadrants.[7] In Situs invertus

totalis (SIT) and MM conditions in which the middle intestine and thus the cecum and appendix vermiformis are atypically localized, pain is felt in the left lower quadrant with clinical differentiation. In our patient, the clinical and physical examination findings were that the typical right-located AA was seen symmetrically on the left side.

MM is a fetal anomaly caused by incomplete or failed rotation of the middle intestine, which is rare during embryonic development.[8] It is classified into three main types, including non-rotation (type I), duodenal malrotation (type II), and combined duodenal and cecal malrotation (type III), depending on the stage at which the embryologic defect occurs.[9] The patient presented in our study was also of the non-rotation type (type I). When the diagnosis of appendicitis is delayed in these cases, complications such as perforation and subsequent abscess formation may occur, which may worsen the clinical course of the patient and complicate the operation.[10]

In patients presenting to the emergency room with left lower quadrant pain, surgeons primarily focus on diverticular disease, gynecologic, or urologic pathologies.[2] If a previous diagnosis of SIT or MM is not known in patients, AA is usually not considered among the initial diagnoses. Because of the anatomical displacement of the heart, stomach, and liver in patients with SIT, the diagnosis is suspected with a chest radiograph and Ultrasonography (USG), which are the first imaging methods, and the diagnosis of AA may be suspected because the appendix is thought to be located on the left side. However, since intra-abdominal and intra-thoracic organs will also be located normally in patients with MM, as in our case, the diagnosis of AA is very difficult according to the results of direct radiography and USG, which are the first imaging methods. Computed tomography (CT), which has a diagnostic value of 90% in the diagnosis of AA, has diagnostic importance in these patients.[7] Our patient was diagnosed with malrotation and AA in an external center as a result of a good anamnesis, physical examination, leukocytosis, and CT imaging.

After the diagnosis of AA is made in patients with MM, open surgery or laparoscopy can be performed depending on the surgeon's experience and technical possibilities.[11] The laparoscopic treatment option was applied in our case because of the advantage of providing a better exploration during surgical treatment with laparoscopy, excluding other pathologies causing left lower quadrant pain, although AA was diagnosed despite the high sensitivity of the CT scan, and considering the possibility of anatomical variation of the appendix.

CONCLUSION

In patients presenting to the emergency room with left lower quadrant pain, it should be kept in mind that AA may rarely be associated with MM. The diagnosis should be made rapidly by using appropriate imaging methods, and treatment should not be delayed. The patient should be informed about the existing malrotation.

ETHICAL DECLARATIONS

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

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

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