Xanthogranulomatous Cholecystitis and Gallbladder Cancer: Two Diseases with Difficult Differential Diagnoses

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ABSTRACT

Background: *Xanthogranulomatous cholecystitis (XGC) etiology has not yet been precisely determined; it is often confused with gallbladder cancer (GBC) in the differential diagnosis.*

Methods:: *This study retrospectively evaluated patients who underwent surgery with the pre-diagnosis of cholelithiasis, cholecystitis, or gallbladder carcinoma at a tertiary center, and were confirmed to have XGC or GBC according to the histological examinations.*

Results: *In the GBC group, there was a higher number of female patients, patients with magnetic resonance imaging (MRI) and computed tomography (CT) imaging, those that directly underwent open surgery, and those requiring catheters and developed complications; while in the XGC group, there was a higher number of patients with ultrasonography (USG) imaging and those requiring conversion from laparoscopic to open surgery ($P < .05$). The rate of patients with a preoperative diagnosis of cholelithiasis was higher in the XGC group than in the GBC group, and cases with intrahepatic bile duct (IHBD) dilatation were higher in the GBC group than in the XGC group, and the GBC group also had a higher rate of cases with a malignant diagnosis in the preoperative examination compared to the XGC group ($P < .05$).*

Conclusion: *When a suspicious malignant mass is detected in the localization of the gallbladder, XGC must be considered in the differential diagnosis. Although it is not a malignant pathology, early diagnosis and treatment are particularly important due to the associated complications and the possibility of coexistence with GBC.*

Keywords: *Xanthogranulomatous cholecystitis, gallbladder cancer, diagnosis*

INTRODUCTION

Xanthogranulomatous cholecystitis (XGC) is a rare chronic inflammatory disease of the gallbladder that is considered to be a variation of chronic cholecystitis. Histologically, it is characterized by pronounced, progressive fibrosis and the accumulation of lipid-laden macrophages in the gallbladder wall, which may spread to the surrounding tissues, including the porta hepatis and the gallbladder fossa in the liver. Almost all cases present with gallbladder stones.[1] XGC is seen 8 to 10 times more often in women than in men.[2] Since XGC has findings similar to those of acute cholecystitis, a differential diagnosis is recommended, to exclude gall bladder carcinoma.[3] The mechanism of formation of XGC has not yet been clearly elucidated; however, the preliminary cause is considered to be the extravasation of bile into the gallbladder wall as a result of the involvement of the Rokitansky–Aschoff sinuses or the progression of a small mucosal ulcer. The presence of gallstones or a biliary obstruction plays an important role in the development of XGC.[4] Physical examination and laboratory findings are not sufficient to distinguish XGC from other gallbladder pathologies. Similar to cholecystitis caused by other reasons, symptoms, and findings such as nausea, vomiting, right upper quadrant pain, positive sonographic Murphy's sign, and leukocytosis can be seen.[5] XGC is often confused with gallbladder carcinoma. It has been reported that unnecessary and large-scale resection procedures have been performed in some XGC cases misdiagnosed as gallbladder carcinoma in the preoperative radiological examination. An accurate diagnosis can usually be made after the histological evaluation.[4]

Gallbladder cancer (GBC), on the other hand, is rare cancer and in seen at a rate of 3 per 100 000 worldwide.[6] The presence of gallstones, advanced age, sclerosing cholangitis, and porcelain sac are the best-known risk factors of GBC. Currently, only one-third of GBC cases can

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be diagnosed in the preoperative period.[7] In most cases, a definitive diagnosis can be made based on a histopathological examination following laparoscopic cholecystectomy undertaken due to the presence of benign pathologies including XGC, and this group has the best prognosis.[8]

As in XGC, chronic inflammation has been reported to be the most important risk factor for GBC. The presence of inflammation has a negative effect on prognosis, since it is also associated with perioperative perforation and the spread of bile into the abdominal cavity.[9] To our knowledge, there are only a few studies in the literature comparing cases of XGC and GBC. In this study, patients who underwent surgery with the pre-diagnosis of cholelithiasis, cholecystitis, or gallbladder carcinoma and were diagnosed with XGC or GBC based on the pathology report were compared in terms of preoperative, intraoperative, and postoperative diagnoses, treatments, and complications.

MATERIALS AND METHODS

The study was conducted with 139 individuals. Patients who had presented to the General Surgery Clinic between January 2013 and December 2018 with the preoperative diagnosis of cholelithiasis, cholecystitis, or gallbladder carcinoma, had undergone surgery, and had been confirmed to have XGC or GBC based on the histopathological results were retrospectively evaluated in terms of demographic characteristics, anamnesis, laboratory examinations, radiological findings, attack history, the requirement of conversion from laparoscopic to open surgery, the use of catheters, complications, length of hospital stay, endoscopic retrograde cholangiopancreatography (ERCP) history, emergency/elective surgery rates, preoperative diagnoses, and presence of intrahepatic bile duct (IHBD) dilatation. In addition, for the patients with GBC, the differentiation degree, tumor stage, tumor diameter, and perineural invasion parameters were also assessed. Patients with gallbladder metastases due to other organ malignancies were excluded from the study.

MAIN POINTS

- *Xanthogranulomatous cholecystitis (XGC) is a rare pathology that can be confused with gallbladder cancer (GBC).*
- *It is important to diagnose XGC preoperatively and intraoperatively.*
- *In XGC cases, with the correct diagnosis, unnecessarily extended resections, increased morbidity, and mortality are prevented.*

Statistical Analysis

The data were transferred to the IBM SPSS Statistics program, Version 23, for analysis. When evaluating the study data, frequency distribution (number and percentages) were used for the categorical variables and descriptive statistics (median, minimum, and maximum) for the numerical variables, depending on the results of the Kolmogorov–Smirnov normal distribution test. The Mann–Whitney *U*-test was used to determine whether there was a difference between the 2 groups, the Kruskal–Wallis test for the difference between more than 2 groups, and the chi-square test to examine the relationship between 2 categorical variables.

RESULTS

The study was divided into 2 groups as XGC and GBC. The median values of age and length of hospital stay were higher in the GBC group than in the XGC group ($P < .001$). There was no statistically significant correlation between the groups in terms of magnetic resonance cholangio pancreatography (MRCP) imaging status and attack history ($P > .05$). The number of female patients was higher in the GBC group, the number of patients with ultrasonography (USG) imaging was higher in the XGC group, and the rate of those with magnetic resonance imaging (MRI) and computed tomography (CT) imaging was higher in the GBC group ($P < .05$). The number of patients requiring conversion from laparoscopic surgery to the open method was higher in the XGC group, the number of those who directly underwent open surgery was higher in the GBC group ($P < .001$), and the number of those requiring catheters and developed complications was higher in the GBC group ($P < .05$) (Table 1).

There was no significant difference between the groups in terms of the median values of postoperative alanine aminotransferase (ALT), preoperative aspartate aminotransferase (AST), preoperative gamma-glutamyl transferase (GGT), preoperative white blood cells (WBC), pre/postoperative amylase, and pre/postoperative lipase ($P > .05$). However, the median values of preoperative ALT, postoperative AST, postoperative GGT, pre/postoperative ALP, pre/postoperative total bilirubin (T.Bil), pre/postoperative direct bilirubin (D.Bil), pre/postoperative C-reactive protein (CRP), and postoperative WBC were significantly higher in the GBC group, and the median alpha-fetoprotein (AFP) was significantly higher in the XGC group ($P < .05$) (Table 2).

While there was no statistically significant correlation between the groups and the ERCP status ($P > .05$), the

Table 1. Differences in Descriptive Statistics Between the Study Groups

	GBC		XGC			
	N	%	*N*	%	Test	*P*
Age, median (min-max)	69 (31-89)		56 (22-85)		−4.106[m]	**<.001**
Gender						
Male	15	29.4	44	50.0	5.602[k]	**.018**
Female	36	70.6	44	50.0		
Imaging method						
USG	48	94.1	88	100.0	5.291[k]	**.048**
MRI	10	19.6	4	4.5	8.088[k]	**.004**
CT	21	41.2	18	20.5	6.869[k]	**.009**
MRCP	0	0.0	4	4.5	2.387[k]	.296
Attack history						
Present	23	45.1	43	49.4	0.241[k]	.623
Absent	28	54.9	44	50.6		
Surgical method						
Laparoscopic	23	45.1	73	83.0	26.089[k]	**<.001**
Open	17	33.3	4	4.5		
Conversion from laparoscopic to open surgery	11	21.6	11	12.5		
Catheter requirement						
Yes	42	82.4	58	65.9	4.325[k]	**.038**
No	9	17.6	30	34.1		
Complications						
Present	9	17.6	2	2.3	10.473[k]	**.002**
Absent	42	82.4	86	97.7		
Length of hospital stay, median (min-max)	4 (1-18)		2.5 (1-15)		−4.718[m]	**<.001**

[m]Mann–Whitney *U*-test; k, chi-square test.

rate of those with cholelithiasis diagnosed in the preoperative examination was higher in the XGC group compared to the GBC group, the rate of those with a preoperative malignant diagnosis was higher in the GBC group compared to the XGC group, and the rate of patients with IHBD dilatation was higher in the GBC group than in the XGC group ($P < .001$) (Table 3). In the GBC group, 23.5% of the patients had poor differentiation, while it was good in 33.3%. While the T stage of 25.5% of the patients was T1, it was T2 in 43.1 % of the patients, and T3 in 31.4% of the patients. The mean tumor diameter was 2 cm (Table 4).

In the GBC group, there was no statistically significant relationship between the preoperative diagnosis and the median values of attack history, the requirement of conversion to open surgery, and length of hospital stay ($P > .05$) (Table 5). Finally, in the XGC group, no statistical relationship was observed between the preoperative diagnosis and the median values of attack history, requirement of conversion to open surgery, emergency surgery rate, and length of hospital stay ($P > .05$) (Table 6).

DISCUSSION

Xanthogranulomatous inflammation is a destructive inflammatory process that may be chronic, focal, or diffuse. It is histologically characterized by a large number of histiocytes and acute inflammatory cells. In the literature, the kidneys, salivary glands, bones, vagina, endometrium, bladder, stomach, and gallbladder have been defined as

Table 2. Differences in Parameter Measurements between the Study Groups

	GBC	XGC		
	Median (min-max)	Median (min-max)	Test	*P*
ALT (Preop)	22 (8-745) U/L	30.5 (9-926) U/L	2.354[m]	**.019**
ALT (Postop)	35 (4-278) U/L	28 (5-214) U/L	–1.294[m]	.196
AST (Preop)	24 (10-689) U/L	29.5 (5-380) U/L	1.285[m]	.199
AST (Postop)	38 (12-940) U/L	27 (7-230) U/L	–3.393[m]	**.001**
GGT (Preop)	46 (11-1928) U/L	40.5 (7-1021) U/L	–1.086[m]	.277
GGT (Postop)	64 (10-952) U/L	40 (8-509) U/L	–2.964[m]	**.003**
ALP (Preop)	104 (44-766) U/L	88.5 (35-846) U/L	–2.000[m]	**.046**
ALP (Postop)	96 (37-1479) U/L	76 (34-690) U/L	–2.841[m]	**.004**
Bilirubin (preop) T. bil	1.1 (0.4-30.2) mg/dl	0.6 (0.2-10.4) mg/dl	–6.375[m]	**<.001**
Bilirubin (Postop) T. bil	0.7 (0.2-25) mg/dl	0.3 (0.1-7.8) mg/dl	–5.742[m]	**<.001**
Bilirubin (preop) D. bil	1.8 (0.6-12.1) mg/dl	0.6 (0.2-8) mg/dl	–6.950[m]	**<.001**
Bilirubin (postop) D. bil	0.7 (0.3-9.2) mg/dl	0.3 (0.1-2.6) mg/dl	–6.525[m]	**<.001**
CRP (Preop)	12 (0.5-309)	3 (0.4-224)	–5.359[m]	**<.001**
CRP (Postop)	56 (1-333)	5.2 (1-185)	–6.805[m]	**<.001**
WBC (Preop)	7.5 (4.3-35.3)	8.6 (3-24)	0.622[m]	.534
WBC (Postop)	10.9 (3.4-31)	8 (3.4-16.1)	–3.187[m]	**.001**
AFP	3 (0.6-371) microg/L	16 (3-32) microg/L	7.515[m]	**<.001**
Amylase (Preop)	52 (12-465) U/L	53.5 (12-601) U/L	0.129[m]	.897
Amylase (Postop)	61 (13-689) U/L	58.5 (13-843) U/L	–0.122[m]	.903
Lipase (Preop)	53 (28-456) U/L	47 (13-2551) U/L	–1.768[m]	.077
Lipase (Postop)	65 (24-298) U/L	64 (12-5343) U/L	–0.796[m]	.426

[m]Mann–Whitney *U*-test.

Table 3. Differences in Variables between the Study Groups

	GBC		XGC			
	N	%	*N*	%	Test	*P*
ERCP						
Absent	42	82.4	71	80.7	0.059[k]	.808
Present	9	17.6	17	19.3		
Preoperative examination diagnosis						
Cholelithiasis	9	17.6	40	45.5	29.881[k]	**<.001**
Acute gallbladder disease	22	43.1	44	50.0		
Malignancy	20	39.2	4	4.5		
IHBD						
Normal	27	55.1	83	94.3	30.590[k]	**<.001**
Dilated	22	44.9	5	5.7		

[k]Chi-square test.

Table 4. Differentiating Findings of GBC

	GBC	
	N	%
Differentiation degree		
Poor	12	23.5
Moderate	22	43.1
Good	17	33.3
Tumor stage		
1	13	25.5
2	22	43.1
3a	11	21.6
3b	5	9.8
Perineural invasion		
Absent	25	49.0
Present	26	51.0
Tumor diameter (cm), median (min-max)	2.0 (0.1-5.5)	

Table 5. Differences in Variables According to Preoperative Diagnosis in GBC Cases

	Preoperative Diagnosis							
	Cholelithiasis		Acute Gallbladder Disease		Malignancy			
GBC	*N*	%	*N*	%	*N*	%	Test	*P*
Attack history								
Present	6	66.7	9	40.9	8	40.0		
Absent	3	33.3	13	59.1	12	60.0		
Surgical method								
Laparoscopic	5	55.6	15	68.2	3	15.0		
Open	0	0.0	5	22.7	12	60.0		
Conversion from laparoscopic to open surgery	4	44.4	2	9.1	5	25.0		
Length of hospital stay, median (min-max)	3.0 (1-14)		3.5 (1-18)		5.0 (2-11)		2.741[w]	.254

[w]Kruskal–Wallis test.

areas where this inflammation has been observed.[2] XGC is a rare form of chronic cholecystitis, which was first described by McCoy in 1976, and is seen in 1.3-5.2% of resected gall bladder specimens.[10] Although the exact etiology of XGC remains unknown, it is considered to occur through the extravasation of bile into the gallbladder wall in the presence of gallstones, obstruction, and cholestasis. It begins as an inflammatory process, with the involvement of the Rokitansky–Aschoff sinuses, and then progresses to a granulomatous reaction that can lead to the formation of a submucosal abscess. XCG is macroscopically characterized by the formation of numerous yellowish nodules within the gallbladder wall.[11] As a result of serosal perforation of the gallbladder and the spread of inflammatory response, XGC can cause adhesions with the surrounding organs, such as the liver, duodenum, and

Table 6. Differences in Variables According to Preoperative Diagnoses in XGC Cases

	Preoperative Diagnosis							
	Cholelithiasis		Acute Gallbladder Disease		Malignancy			
XGC	*N*	%	*N*	%	*N*	%	Test	*P*
Attack history								
Present	15	37.5	25	58.1	3	75.0		
Absent	25	62.5	18	41.9	1	25.0		
Emergency surgery								
Present	10	25.0	19	43.2	1	25.0		
Absent	30	75.0	25	56.8	3	75.0		
Surgical method								
Laparoscopic	34	85.0	36	81.8	3	75.0		
Open	0	0.0	3	6.8	1	25.0		
Conversion from laparoscopic to open surgery	6	15.0	5	11.4	0	0.0		
Length of hospital stay, median (min-max)	2.0 (1-15)		3.0 (1-5)		3.0 (2-4)		0.948[w]	.623

[w]Kruskal–Wallis test.

transverse colon. The close similarities between XGC and GBC may be responsible for more than 1 in 10 patients being treated with unnecessary extended resection or having a missed cancer. In such cases, it is important to carefully evaluate the clinical symptoms and radiological features of XGC in order to avoid unnecessary radical surgery and prevent morbidity.[12] Unfortunately, the clinical indications of XGC are very similar to acute and/or chronic cholecystitis, and there are no specific signs or symptoms in the differential diagnosis.[13] At the same time, it is considered that the clinical characteristics of patients offer little benefit in distinguishing XGC from GBC.[11]

Although the radiological findings of XGC bear much resemblance to GBC in terms of gallbladder wall thickening and the tendency to involve neighboring organs, the presence of gallstones is very high in XGC cases, compared to GBC. In XGC, it is important to observe the thickening of the gallbladder wall and the presence of gallstones or sludge. European studies have reported the incidence of gallstones in XGC to vary between 92% and 100%.[12] Uchiyama et al. reported that diffuse wall thickening and intramural nodule formation in the gallbladder on USG were pathognomonic for XGC.[4] Although we found gallstones in 97.75% (n = 87) of our XGC cases using hepatobiliary USG, only 6.74% of the cases had intramural nodules. This situation may be related to the level of experience of radiologists performing the procedure in relation to the diagnosis of XGC. In XGC, severe proliferative fibrosis can also lead to the hardening of the gallbladder wall, infiltration of the liver parenchyma, and dense adhesions with the colon, duodenum, and stomach, which can easily be confused with GBC in preoperative radiological and intraoperative examinations. In such cases, the presence of infiltration findings in the surrounding organs during surgery may result in extensive radical surgical procedures, lymphadenectomy, and bowel resection. For the ideal approach in XGC, the patient's history, physical examination findings, radiological findings, and preoperative cytology, if any, should be carefully evaluated. Rarely, some patients may experience symptoms such as anorexia and weight loss, suggesting malignancy.[13]

In XGC, the thickening of the gallbladder wall is the most common CT finding. Gallstones can be identified on CT. The gallbladder mucosa shows homogeneous contrast enhancement. Similar findings are observed in MRI. However, neither CT nor MRI is a specific examination to diagnose XGC.[5] Complications such as perforation, abscesses, and fistulas can occur in 32% of cases with XGC, and in some patients, XGC can coexist with GBC.[14] In our study, a preoperative CT was performed in 20.5% of our XGC cases, and perforation and abscesses were detected in 22.2% of the patients who underwent CT. The early diagnosis of XGC is important, especially due to the frequency of its complications and the possibility of coexistence with carcinoma. As in GBC, a marked thickening of the wall is also seen in XGC. Detecting intramural nodules on CT can help diagnose XGC. Complications usually occur in the acute period.[14] In many studies, the presence of a hypodense nodule involving more than 60% of a thickened gallbladder wall in USG and CT examinations is considered to be significant for XGC in the differential diagnosis. The demonstration of the presence/absence or continuity/interruption of the mucosal line formed together by the gallbladder mucosa and the muscle layer on CT is a finding that can be used to distinguish between XGC and GBC. It has been shown that the continuity of this line is disrupted by 100% in GBC, while it is preserved at a rate of 64% in XGC.[15] Nevertheless, as mentioned above, the most important factor in diagnosis is the radiologist who evaluates the CT, primarily considering the XGC diagnosis, and being experienced in the field. Khan et al. found hypoechoic nodules (73%) and bands (19%) in the thickened gallbladder wall in the CT images of XGC cases.[16] Zhoa et al. observed intramural nodules at a rate of 85.7% and 61.1%, in the CT of XGC and GBC cases, respectively.[17] In our study, the rates were lower than in the literature (33.3% for XGC and 23.8% for GBC). Luminal surface enhancement (LSE), which is a characteristic feature of XGC in the portal venous phase, was observed in 85.7% of cases. In addition, in these cases, organ infiltrations including fistulae and abscesses in the liver, colon, and duodenum were observed on CT. The MRI findings supporting XGC were wall thickening outside the foci, presence of intramural nodules, and LSE. T2-weighted images showing isointense to slightly hyperintense signal areas on MRI are also compatible with the presence of xanthogranulomas (XG).[16] In our study, intramural nodules were observed in one patient who underwent MRI in the XGC group. While gallbladder wall thickening is more common in XGC cases, focal wall thickening is more frequently observed in GBC. However, this finding is not sufficient to distinguish between XGC and GBC. Other findings, such as liver involvement, lymphadenopathy, biliary obstruction, and pericholecystic infiltration can help differentiate XGC from GBC. The presence of significantly large lymph nodes around the gall bladder, heterogeneous in appearance, numerous, and having the appearance of a heterogeneous and

irregular liver mass, especially in the area close to the gallbladder, should primarily suggest GBC.

Parra et al. argued that USG successfully demonstrated gallstones and focal/diffuse wall thickening but was able to detect only 35% of the hypoechogenic nodules and bands considered to be typical features of XGC. These findings are also valid for intramural abscesses and adenomyomatosis.[18] Therefore, the CT criteria are of particular importance when distinguishing between GBC and XGC. Goshima et al. suggested that diffuse wall thickening, continuity of the mucosal line, presence of intramural hypoattenuating nodules, and absence of the invasion of the adjacent liver parenchyma, and IHBD dilatation confirm the diagnosis of XGC with sensitivity and specificity rates of 83-100%.[19] We observed IHBD dilatation in 44.9% of the patients in the GBC group, while in 5.7% of those in the XGC group.

Currently, there are 2 important problems facing the surgeon in the diagnosis of XGC: to avoid missing GBC that requires radical surgery, and to completely reveal the duration of the surgical dissection procedure, complication rate, and type of cholecystectomy, such as open vs. laparoscopic and full vs. partial.[20] The metaplasia–dysplasia–neoplasia inflammatory phenomenon sequence is assumed to be effective in XGC. Moreover, in 30% of GBC cases, focal XG changes defined as neoplastic have been shown in the gallbladder wall. Therefore, an intraoperative frozen section examination is recommended by some authors.[19] However, in daily practice, the possibility of conducting this type of analysis may be limited in some medical centers, especially in cases where cholecystectomies are performed under emergency conditions.

In a study conducted by Kwon et al.,[21] the rate of conversion to open surgery during laparoscopic cholecystectomy was found to be 19-80% in XGC cases.[21] Günes et al. considered surgery for XGC to be difficult due to its radiological, clinical, and intraoperative characteristics that mimic GBC, and stated that conversion to open cholecystectomy might be necessary due to the difficulties in laparoscopic dissection during the operation. However, since the conversion cholecystectomy rates were at a reasonable level, the authors recommended laparoscopic surgery in patients with suspected XGC.[22] In our cases, the rate of conversion from laparoscopic to open surgery was 26.1% in the GBC group and 12.5% in the XGC group.

Endoscopic ultrasound-guided fine-needle aspiration cytology (EUS-FNAC) can be a convenient and safe method for sampling gallbladder lesions that cannot be clearly differentiated radiologically. As mentioned above, some authors estimate that XGC and GBC coexist in 12% of patients. Therefore, even if a preoperative diagnosis of XGC is made using FNAC, the possible association between XGC and cancer in the same gallbladder should not be forgotten.[23] Although the diagnostic accuracy of FNAC is around 96%, it is not clear whether there is a tumor on the non-sampled surfaces in the gallbladder. The procedure also has the additional risk of fistula formation from tumor tissue and tumor seeding along the tract.[24] In line with this information, we did not use FNAB for the differential diagnosis in our cases. Currently, an intraoperative frozen section examination is one of the best methods for distinguishing between XGC and GBC in suspected cases. Unnecessary radical interventions and complications can be prevented by performing this examination during the operation.[25] In our study, the frozen section examination was undertaken in 21.5% of the patients with GBC and 12.5% of those with XGC. In addition, although the preoperative and postoperative ALP, T.Bil, D.Bil ,CRP, and postoperative WBC values were observed at a higher rate in the GBC patients compared to the XGC patients, it was determined that the above mentioned biochemical parameters alone would not be sufficient in the differential diagnosis, and further studies with larger series are needed to support the findings. Concerning XGC therapy, the surgeon should approach GBC with a high degree of skepticism.

CONCLUSION

XGC should be taken into account in the differential diagnosis when a suspicious malignant mass is detected in the localization of the gallbladder. Although XGC is not a malignant pathology, early diagnosis and treatment are very important due to complications that may occur in the future, and its possible coexistence with GBC. We consider that as the experience of both the surgeon and the radiologist increases in the differentiation of XGC and GBC cases, a healthier differential diagnosis can be made and unnecessary interventions can be avoided.

Ethics Committee Approval: The study was approved by the ethical committee of Ankara Numune Education and Research Hospital (E-19-2482).

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