Cukurova Medical Journal
ÇUKUROVA ÜNİVERSİTESİ TIP FAKÜLTESİ

Cukurova Med J 2021;46(4):1351-1359
DOI: 10.17826/cumj.976851

ARAŞTIRMA / RESEARCH

Effect of xanthogranulomatous cholecystitis on surgery

Ksantogranülomatöz kolesistitin cerrahi üzerine etkisi

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Cukurova Medical Journal 2021;46(4):1351-1359

Abstract

Purpose: The aim of this study is to evaluate the incidence of pathologies causing biliary stasis together with xanthogranulomatous cholecystitis (XGC) and its effect on conversion to open cholecystectomy.
Materials and Methods: This retrospective study reviewed the medical records of 11840 patients who underwent cholecystectomy at Seyhan State Hospital between January 2010 and June 2020. After examining the medical records, 40 (0.33%) of 11840 cholecystectomy cases were diagnosed as XGC pathologically.
Results: In the last decade, 40 (0.33%) patients out of a total of 11840 patients who underwent cholecystectomy were diagnosed with XGC. The mean age of the cases was 58 (34-88). In 26 (65%) of 40 patients, surgery was completed laparoscopically. Open surgery was performed in 5 (12.5%) of them. Nine (22.5%) patients were converted from laparoscopic cholecystectomy to open surgery. In all cholecystectomy cases, the conversion cholecystectomy(CC) rate was 412/11840 (3.4%). Endoscopic retrograde cholangiopancreatography(ERCP) was performed in 13 (32.5%) patients for diagnosis and therapeutic purposes related to bile ducts. The gallbladder wall's average thickness was found to be 8.0 millimeters (± 3.87) on histopathological examination. 38 (95%) patients had an increase in gall bladder wall thickness of 4 millimeters or more. CC rate was found to be high in the subgroup analysis of pathology causing bile stasis and in patients who underwent emergency cholecystectomy.
Conclusion: This study demonstrates that the pathologies causing bile stasis are observed more frequently in XGC patients than other cholecystitis patients, suggesting that these pathologies may be associated with XGC.
Keywords: Conversion cholecystectomy, gallbladder, laparoscopy, xanthogranulomatous cholecystitis

Öz

Amaç:. Bu çalışmada biliyer staza neden olan patolojilerin ksantogranülomatöz kolesistit (XGC) ile birlikte görülme sıklığı ve konversiyon kolesistektomiye etkisinin değerlendirilmesi amaçlanmıştır.
Gereç ve Yöntem: Bu retrospektif çalışmada Ocak 2010-Haziran 2020 tarihleri arasında Seyhan Devlet Hastanesi'nde kolesistektomi yapılan 11840 hastanın tıbbi kayıtları incelendi. Tıbbi kayıtlar incelendikten sonra patolojik olarak XGC tanısı alan hastalar çalışmaya dahil edildi.
Bulgular: Son on yılda kolesistektomi yapılan toplam 11840 hastanın 40'ına (%0.33) XGC tanısı kondu. Olguların yaş ortalaması 58 (34-88) idi. 40 hastanın 26'sında (%65) ameliyat laparoskopik olarak tamamlandı. Bunların 5'ine (%12,5) açık cerrahi uygulandı. Dokuz (%22.5) hastada laparoskopik kolesistektomiden açık cerrahiye geçildi. Tüm kolesistektomi olgularında konversiyon kolesistektomi(KK) oranı 412/11840 (%3.4) idi. Safra yolları ile ilgili tanı ve tedavi amaçlı 13 (%32.5) hastaya endoskopik retrograd kolanjiyopankreatografi (ERCP) yapıldı. Histopatolojik incelemede safra kesesi duvar kalınlığı ortalama 8,0 milimetre (± 3,87) olarak bulundu. 38 (%95) hastada duvar kalınlığında 4 milimetre veya daha fazla artış vardı. Safra stazına neden olan patolojinin alt grup analizinde ve acil kolesistektomi yapılan hastalarda KK oranı yüksek bulundu.
Sonuç: Bu çalışma ışığında XGC hastalarında safra stazına neden olan patolojilerin diğer kolesistit hastalarına göre daha sık görülmesi bu patolojilerin XGC etiyolojisi ile ilişkili olabileceğini düşündürmektedir.

Anahtar kelimeler: Konversiyon kolesistektomi, ksantogranülomatöz kolesistit, laparoskopi, safra kesesi

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Geliş tarihi/Received: 31.07.2021 Kabul tarihi/Accepted: 09.09.2021 Çevrimiçi yayın/Published online: 17.09.2021

INTRODUCTION

Xanthogranulomatous cholecystitis (XGC) is a rare disease in which the gallbladder is affected by focal or diffuse inflammatory processes[1]. Acute inflammation in XGC is followed by a granulomatous reaction and a cellular-type immune response[2,3]. Rokitansky-Aschoff sinuses or mucosal ulcers ruptured by bile penetration into the gallbladder wall cause a chronic inflammatory process. In addition, there is an accumulation of lipid-laden macrophages in the submucosal space. All these events are thought to be effective in the etiopathogenesis of XGC. The most affected patient group is middle-aged women with gallstones. Its incidence has been reported as 0.7-9.0%[4,5]. Because of its close relationship with gallstones, it frequently causes inflammatory spread towards the liver. Therefore, XGC may be radiologically confused with gallbladder cancer, leading to unnecessary radical surgery.

Although XGC and gallbladder cancer are differentiated clinically and radiologically, histological evaluation is the gold standard approach. Surgical procedures are technically difficult due to severe fibrosis and adhesions to surrounding tissues. Therefore, laparoscopic cholecystectomy (LC), the gold standard technique in treating benign gallbladder diseases, cannot be easily performed in XGC patients. Furthermore, unsuccessful and long operation times often causes complications and increased conversion rates from laparoscopic procedure to open cholecystectomy (OC) [5].

This study aimed to evaluate the frequency of XGC and biliary stasis, biliary stasis subtypes, and the effect of surgery performed under emergency or elective conditions on conversion cholecystectomy (CC). CC rates were high in emergency cholecystectomies of patients with XCG diagnosis and in the presence of pathologies causing stasis the distal bile ducts. It was observed that pathologies causing distal bile duct stasis had an effect on CC in subgroup evaluations.

MATERIALS AND METHODS

Procedure

In this retrospective study, we examined the medical records of 11840 patients who underwent cholecystectomy at Seyhan State Hospital between January 2010 and June 2020. Patient information is stored in the written document and digital data recording system. After reviewing the medical records, among the 11840 cholecystectomy cases, 40 (0.33%) patients were diagnosed with XGC pathologically. Patients with uncertain XGC diagnosis in the pathology report and patients younger than 18 years of age were not included in the study. The presence of gallbladder stones, wall thickness, intraluminal or intramural mass was examined. In addition, the presence of bile duct enlargement, bile sludge or stones in the bile ducts, history of endoscopic retrograde cholangiopancreatography (ERCP), common bile duct anomalies and other causes of chronic inflammation were investigated. Data on age, gender, clinical features, accompanying jaundice, elevated liver enzymes, intraoperative findings, and postoperative complications were collected. Histopathological examination of XGC revealed exanthema cells (histiocytes containing lipid and bile pigment), giant multinucleated histiocytes, and acute or chronic inflammatory cells.

For the study, an ethical approval numbered 1101/68/21.10.2020 was obtained by applying to the Adana City Hospital ethics committee.

Patient selection

Seyhan State Hospital, where this study was conducted, is a health center that frequently performs cholecystectomy. For cholecystectomy, patients are operated after the outpatient preparation process. Cholecystectomy is planned in the first 48 hours after the procedure for patients who require ERCP. Cholecystectomy is planned 6 weeks after ERCP for patients who cannot undergo cholecystectomy in the first 48 hours. Generally, the operation is performed with a single general surgeon and surgical team. Four-trocar laparoscopic cholecystectomy is performed as the standard approach in patients undergoing planned cholecystectomy. Open surgery is performed in patients who has a high risk of bile duct injury and cannot be operated safely. The operations are performed by surgeons experienced in laparoscopic and open cholecystectomy surgeries.

Radiological evaluation

A preoperative radiological examination and evaluation of outpatient and emergency patients is performed by a radiologist. The presence of gallstones are examined by preoperative ultrasonography (USG) evaluation. Patients with suspected gallstones or biliary sludge in the common

biliary tract is examined with Magnetic Resonance Imaging (MRI). A diagnosis of biliary tract anomaly was made with MRI and ERCP examinations.

Laboratory tests

Hemoglobin, alkaline phosphatase, alanine transferase, aspartate transferase, total bilirubin, direct bilirubin, C reactive protein, gamma-glutamyl transferase, hematocrit, and white blood cell levels of the patients were evaluated before the operation. In emergency surgeries, the laboratory values of the patients are examined 24 hours before the surgery. In elective surgeries, it is evaluated within 30 days at the latest before the surgery. Laboratory tests are repeated if they are older than 30 days.

Statistical analysis

SPSS 23.0 package program was used for statistical analysis of the data. Categorical measures such as emergency and elective surgery, open surgery, laparoscopic surgery, conversion cholecystectomy, distal bile duct pathology, and its subtypes, ERCP, and presence of pancreatitis were calculated as numbers and percentages. Continuous measurements including age, alkaline phosphatase, alanine transferase, aspartate transferase, carbohydrate antigen, carcino embryogenic antigen, c-reactive protein, gamma-glutamyl transferase, hematocrit, white blood cell, and platelet were summarized as mean deviation and minimum-maximum.

The conformity of the variables to the normal distribution was examined using visual (histogram and probability graphs) and analytical methods (Kolmogorov-Smirnov / Shapiro-Wilk Tests). The Chi-square test and Fischer precision test were used to compare categorical variables. The Mann-Whitney U test was used in groups that did not fit the normal distribution. Statistical significance level was taken as 0.05 in all tests.

RESULTS

In the last decade, 40 (0.33%) patients out of a total of 11840 patients who underwent cholecystectomy were diagnosed with XGC. The mean age of the cases was 58 (34-88). Slight male dominance was observed in gender distribution. (22 men and 18 women). The male to female ratio was calculated as 1.22. It was determined that the most common complaint of patients with XGC diagnosis was abdominal pain 31 (77.5%). Gallstones were detected in 34 (85%) patients. The average stone diameter was 10.48 (1-30) millimeters. The patients demographic data and clinical characteristics are shown in table 1. 32 (80%) patients were operated on in elective conditions, 8 (20%) patients were under emergency conditions. Preoperative laboratory values of the patients are examined and shown in table 2.

Carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (Ca 19-9) were not studied in all patients. CEA values were measured in five patients. On histopathological examination, the gall bladder wall average thickness was 8.0 millimeters (± 3.87). 38 (95%) patients had an increase in wall thickness of 4 millimeters or more. All patients were evaluated with abdominal ultrasonography, eight patients with computed tomography (CT), and 11 with MRI. An increase in wall thickness was observed in 24 (60%) patients who underwent USG and all patients evaluated with CT and MRI. Gall bladder malignancy was suspected in the evaluation of 2/40 (5%) on USG, 3/8 (37.5%) on CT, 2/11 (18.1%) on MRI. Open surgery was applied to 4 patients with suspected malignancy, and malignancy was ruled out by performing intraoperative frozen section analysis. Radiological imaging and histopathological findings of the patients are shown in table 3.

Table 1. Demographic data andc linical presentation of cases

Variable	n=40
Age(y)	58.88(34-88)
Male/Female(n)	22/18
Clinical Presentation	
Abdominal Pain	31(77.5%)
Abdominal pain +Jaundice	1(2.5%)
Abdominal pain +Fever	8(20%)
Application method	
Urgent	8(20%)
Elective	32(80%)
Comorbidity of the patient	
HT	12
DM	10
HT + DM	5
Ischemic heart disease	7
Length of stay(d)	3.68±1.97

Variables are presented as mean ± standard deviation, median or n (%). Abbreviations: HT, hypertension; DM, diabetes mellitus.

Table 2. Laboratory findings of cases

Variable	Mean ± sd	Med (Min-Max)
Preop WBC µl/ml	10771.25	10390 (5070-17500)
Platelet mm³	317300	305500 (145000-804000)
HTC	39.71±4.90	41.3 (28.2-46.0)
Pre-op CEA (n:5) ng/mL	2.42±0.24	2.42 (2.3-2.6)
Ca 19.9 (n:7) U/mL	214.08	23.66 (7.2-1200)
Pre-op CRP mg / L	13.48	4 (1-90)
Pre-op Total bilirubin mg/dl	1.01	0.72 (0.15-5.14)
Preop direct bilirubin mg/dl	0.48	0.30 (0.02-3.17)
AST U/L	54.43	22.5 (11-636)
ALT U/L	60.98	27 (6-765)
ALP U/L	105.52	85 (35-326)
GGT U/L	93.0	60 (32-413)
Amylase U/L	62.88	54.5 (20-158)

Laboratory tests were performed between 1 and 30 days before the operation.
Variables are presented as mean ± standard deviation, median. Abbreviations: ALP: Alkaline phosphatase, ALT: Alanine transferase, AST: Aspartate transferase, CA: carbohydrate antigen, CEA: Carcino embryogenic antigen, CRP: C reactive protein, GGT: Gamma-glutamyl transferase HTC: hematocrit, WBC: White blood cell

ERCP was performed in 13 (32.5%) patients for diagnosis and therapeutic purposes related to bile ducts. ERCP was performed in 6 patients for choledocholithiasis and three patients for pancreatitis a few weeks before surgery. 4 patients had elevated bilirubin levels at presentation. Pathologies that impair bile flow in the bile duct and cause bile stasis are shown in table 4. The rate of conversion to open cholecystectomy in all cholecystectomy cases was 412/11840 (3.4%). Surgery was completed laparoscopically in 26 (65%) of 40 patients diagnosed with XGC. Open surgery was performed in 5 (12.5%) of them. Nine (22.5%) patients switched from laparoscopic cholecystectomy to open surgery.

Of the patients who underwent CC, fibrosis of the gallbladder to the surrounding tissues was found in 5, the failure of revealing the Callot's triangle is found in 2 patients, and lateral injury in the common bile duct in 2 patients. In the postoperative period, wound infection was seen in 1 patient, biliary tract injury in 2 patients, biliary fistula in 1 patient, and atelectasis in 2 patients. Biliary tract injuries were treated with T-tube drainage and primary repair in the same session. One patient had bile came from the drain on the first postoperative day and who was thought to have a biliary fistula due to open Luchska's duct in the imaging, was treated with ERCP.

The effects of pathologies causing bile stasis on CC are summarized in table 5. The effect of surgery in emergency and elective conditions on CC rates in XGC patients is shown in table 6. There was no mortality in the early postoperative period in the evaluation made in all patients.

Table 3. Histopathological, Radiological finding (abdominal ultrasonography + contrast-enhanced computed tomography abdomen+ MRI) and operative features.

Variable	n/Median
Preop imaging	
USG	21(52.5%)
USG+CT	8(20.0%)
USG+MRI	11(27.5%)
Common bile duct diameter(mm)	7 (5-12)
Gallstone in the bladder	
Yes	34(85.0%)
No	6(15.0%)
Gallstone type (n=34)	
Cholesterol	31(91.2%)
Pigment	3(8.8%)
Gallbladder wall thickness (mm)	7 (3-18)
Surgical Technique	
Open surgery	5(12.5%)
Laparoscopic surgery	26(65%)
Conversion surgery	9(22.5%)

Variables are presented as median or n (%). Abbreviations: USG, ultrasonography; CT, computed tomography; MRI, magnetic resonance imaging

Table 4 Pathologies in the distal bile ducts causing other pathologies and bile duct stasis

Variable		**N**	**%**
Pathology in the distal biliary tract			
	No	24	60.0
	Double common bile duct anomaly	1	2.5
	Choledocholithiasis	10	25.0
	Mirizzi type 1	2	5.0
	Bile sludge	3	7.5
ERCP History			
	No	27	67.5
	Yes	13	32.5
Pancreatitis History			
	No	33	82.5
	Yes	7	17.5

Variables are presented as n (%). Abbreviations: ERCP, endoscopic retrograde cholangiopancreatography.

Table 5. Operative evaluation of distal bile duct pathologies causing bile stasis

	Operation			**p**
	Open	**Laparoscopic**	**CC**	
	n (%)	n (%)	n (%)	
Distal pathology				0.16
No	3(60.0)	18(69.2)	3(33.3)	
Yes	2(40.0)	8(30.8)	6(66.7)	
Subgroup Analysis				<0.01
No	3(60.0)	18(69.2)	3(33.3)	
Double bile duct anomaly	1(20.0)	0(0.0)	0(0.0)	
Choledocholithiasis	1(20.0)	8(30.8)	1(11.1)	
Mirizzi type 1	0(0.0)	0(0.0)	2(22.2)	
Bile sludge	0(0.0)	0(0.0)	3(33.3)	

Table 6 The effect of emergency and elective operations on the surgical approach

	Operation		p
	Emergency	Elective	<0.01
	n(%)	**n(%)**	
Open	1 (12.5)	4 (12.5)	
Laparoscopic	2 (25.0)	24 (75.0)	
CC	5 (62.5)	4 (12.5)	

DISCUSSION

There are few studies in the literature evaluating biliary stasis in the etiopathogenesis of XGC. On the other hand, Saritas et al. reported that 31.6% of XGC cases had a pathology that caused biliary stasis [6]. Yücel et al. did not emphasize the relationship between conditions causing biliary stasis and XGC in their study. However, they reported that 13.8% of the patients had ERCP, 11.1% had choledocholithiasis, 4.6% had cholangitis, and 4.6% had acute pancreatitis in the preoperative period[7]. In our study, pathologies that may lead to extrahepatic bile duct obstruction were observed in patients diagnosed with XGC[4,6]. Although choledocholithiasis were more common in these patients, biliary sludge, Mirizzi syndrome, and double choledochal anomaly were observed in the common bile duct. CC rates are high in XGC

patients. CC rates increase in the presence of pathological findings causing bile stasis. Our study, determined that CC rates were high in XCG patients with distal bile duct pathology. CC ratios were also evaluated in the subgroup analysis of bile stasis causes, and the difference was statistically significant. On the other hand, the frequent occurrence of pathologies causing biliary stasis in XGC patients suggests that these pathologies may be associated with XGC. Therefore, it would be useful to investigate additional pathologies that may cause bile stasis in the distal bile ducts in patients with suspected XGC.

XGC is a rare disease of the gallbladder that was described 50 years ago[8]. It is a rare type of chronic cholecystitis, the pathogenesis of which is getting better and better every day[9,10]. It is characterized by lipid-loaded immune cell accumulation and proliferative fibrosis in areas of destructive inflammation. XGC often causes increased gallbladder wall thickness[9]. It is difficult to distinguish some cases of XGC from gallbladder cancer because of radiological findings and tumor marker elevation findings[8,11]. Although studies in the literature give the male / female ratio between 1.5 and 5.2, studies report that XGC affects men and women equally[4,12,13]. In our study, the male / female ratio was found to be 1.22, although male dominance was close to each other. Although the signs or symptoms are not specific to XGC, the most common clinical complaints are pain in the right upper quadrant and epigastric region. The clinical symptoms are generally the same as acute or chronic cholecystitis[14]. Patients with XGC may also present with acute cholecystitis complications such as obstructive jaundice, acute biliary pancreatitis, or gall bladder empyema[15]. In our results, 20% (n: 8/40) of the patients were operated on after emergency service admissions. The most common presenting complaint was abdominal pain, with 77.5% (n: 31/40). 13 of our patients had a jaundice history, and 7 had a history of acute pancreatitis.

XGC is a histologically benign and clinically aggressive disease; the clinical significance is the difficulty in distinguishing it from gallbladder cancer[15]. Already, XGC was initially defined as a pseudotumor of the gallbladder[16]. Essential features that help determine XGC from gallbladder cancer are diffuse wall thickening instead of focal thickening, intramural hypo-attenuated nodules with the entire mucosal line, and liver absence involvement[17,18]. In our study, four patients evaluated with a pre-diagnosis of gallbladder tumor in radiological evaluations performed before surgery were identified.

When the articles in the literature are evaluated, the increase in wall thickness in imaging methods is detected between 74.2% and 81.6% of patients. In the study conducted by Park et al., a diffuse wall thickness increase was observed in 74.2% of the patients as a CT finding. It has been emphasized that can better evaluate the mucosa with MRI in the differential diagnosis of XGC and gallbladder cancer[4]. In our study, the wall thickness increase was observed in 75% of the patients evaluated by USG. An increase in gallbladder wall thickness was detected in all patients evaluated with CT and MRI for additional examination (Figure 1).

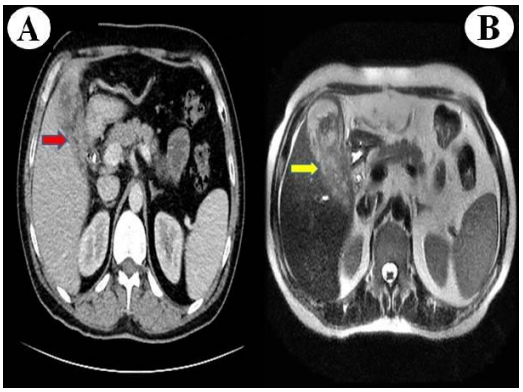

Figure 1. XGC preoperative imaging

a: CT, Multiple hypodense nodules (red arrow) in the widely thickened gallbladder wall. Axial computed tomography section showing gallstones. Computed tomography images show the fundal-corpus region of the gallbladder with diffuse wall thickening with a weak fat plan and infiltration into the adjacent hepatic parenchyma.

b: MRI; Axial T2W image showing multiple gallbladder calculi with a diffusely thickened wall showing multiple intramural nodules (yellow arrow).

The definitive treatment for XGC is surgery. Laparoscopic cholecystectomy, the gold standard surgical method in benign gallbladder diseases, may not always be possible due to increased wall thickness resulting from chronic inflammatory processes in XGC cases. Also, XGC may cause chronic inflammation, deterioration of the gallbladder wall's integrity, border irregularity, advanced fibrotic

adhesions to surrounding structures, and biliary fistulas[19,20](Figure 2).

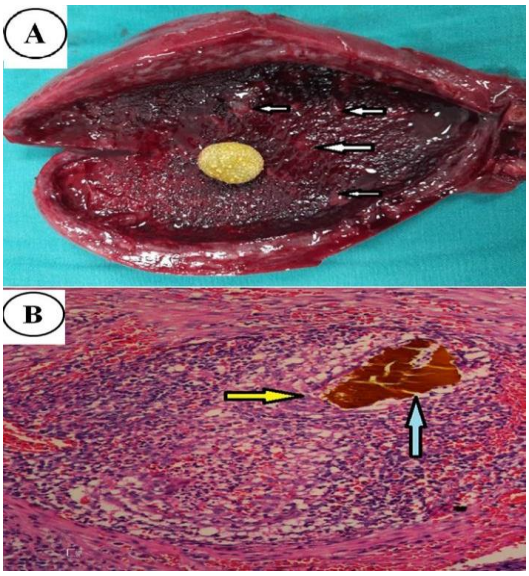

Figure 2. Histopatological and back-table inspection of XGC,

a: Gross pathology specimen; gallblader wall thickness increase and the appearance of penetrating bile into the Wall (White arrows),

b: The appearance of giant inflammatory cells (yellow arrow) around the bile that invades the gallbladder wall and bile (blue arrow) (HE, 200 ×).

For these reasons, some reports state that the laparoscopic method should not be applied to XGC, a benign disease. These studies emphasized that open cholecystectomy could be performed if there is a suspicion of malignancy, and excessive adhesions cannot be dissected[3,9]. It has been reported that a high CC ranging from 10 to 80% can be encountered in laparoscopic surgery of XGC[21,22]. In the study conducted by Park et al., all patients were evaluated by CT scan. The conversion rate was reported to be 16.1% in those with suspected tumors knowing that they had benign pathology using MRI[4]. Qasaimeh et al. In their study, direct open cholecystectomy was preferred in 7 patients with preoperative tumor suspicion. The conversion rate was reported as 31.4% in cases initiated laparoscopically. The same study said that there was ten times more CC in XGC than other cholecystectomies in their series[12]. In the survey conducted by Condilis et al., The conversion rate in all cholecystectomy cases was 9.1%[23]. Qasaimeh et al. The high rate of CC was attributed to the inability to reveal the anatomy and bleed. As we explained in the literature, this justifies the thesis that the chronic inflammation process is more in XGC[12]. In their study by Costantini et al., CC rate was high in patients who underwent ERCP. In this study, subtyping of the pathology results of the patients was not made[24]. In another study, after ultrasonographic evaluation, the gallbladder wall thickness was above 3 mm. It was shown that the presence of gallstones obstructing the bile ducts increased the rates of CC[25]. In our study, the reason for turning laparoscopic surgery to open surgery in 9 (22.5%) patients was excessive fibrosis and difficulty in revealing the anatomy. CC in XGC was 6.6 times higher than CC in all cholecystectomies in our series. Increased gallbladder wall thickness was demonstrated histopathologically in 95% of XGC patients, and ERCP was performed in 32.5% of patients.

Terho et al., in their study on treatment with laparoscopic cholecystectomy in acute stony cholecystitis, the rate of CC was stated as 22.5%. The complication rate was found to be 29.8% in patients who underwent CC[26]. Our study observed that 5 (71.4%) of 7 patients whose laparoscopic surgery was initiated from the emergency department underwent CC. The complication rate in patients who underwent conversion cholecystectomy was 40%. The higher rate compared to other laparoscopic emergency cholecystectomy surgeries in the literature is associated with XGC pathology.

Patients may have postoperative complications such as biliary injury, bile leakage, bleeding, and minor or significant surgical site infections[3,27]. In our study, wound infection in 1 (2.5%), bile duct injury in 2 (5%), biliary fistula in 1 (2.5%), and pulmonary complications developed in 3 (7.5%) patients.

There are some limitations in this study: It is retrospective, the low number of patients in subgroups causing biliary stasis, radiological evaluation, and surgical procedure was performed by different physicians, and tumor markers could not be evaluated in all patients.

)In conclusion, the fact that pathologies causing bile stasis were more common in XGC patients compared to other cholecystitis patients suggested that these pathologies may be related to XGC. However, prospective studies are needed to evaluate the cause-and-effect relationship between the pathologies that cause bile stasis and XGC.

Yazar Katkıları: Çalışma konsepti/Tasarımı: MA, FK; Veri toplama: MA, FK; Veri analizi ve yorumlama: MA, FK; Yazı taslağı: MA, FK; İçeriğin eleştirel incelenmesi: MA, FK; Son onay ve sorumluluk: MA,

FK; Teknik ve malzeme desteği: MA, FK; Süpervizyon: MA, FK; Fon sağlama (mevcut ise): yok.
Etik Onay: Bu çalışma için Adana Şehir Eğitim ve Araştırma Hastanesi Klinik Araştırmalar Etik Kurulundan 21.10.2020 tarih ve 1101/68 sayılı kararı ile etik onay alınmıştır.
Hakem Değerlendirmesi: Dış bağımsız.
Çıkar Çatışması: Yazarlar çıkar çatışması beyan etmemişlerdir.
Finansal Destek: Yazarlar finansal destek beyan etmemişlerdir.
Author Contributions: Concept/Design : MA, FK; Data acquisition: MA, FK; Data analysis and interpretation: MA, FK; Drafting manuscript: MA, FK; Critical revision of manuscript: MA, FK; Final approval and accountability: MA, FK; Technical or material support: MA, FK; Supervision: MA, FK; Securing funding (if available): n/a.
Ethical Approval: Ethical approval was obtained for this study from the Adana City Training and Research Hospital Clinical Research Ethics Committee with the decision dated 21.10.2020 and numbered 1101/68.
Peer-review: Externally peer-reviewed.
Conflict of Interest: Authors declared no conflict of interest.
Financial Disclosure: Authors declared no financial support

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