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Gallbladder perforation: Clinical presentation, predisposing factors, and surgical outcomes of 46 patients

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Background/aims: *We aimed to investigate the clinical features and the relation between patient characteristics and the different types of gallbladder perforation and to determine the predisposing factors.* ***Material and Methods:*** *The medical records of 478 patients who received urgent surgical treatment with the diagnosis of acute cholecystitis and underwent urgent surgery in our clinics between January 1997 and November 2008 were reviewed retrospectively. The demographic data of patients, time elapsed from the onset of the symptoms to the time of surgery, comorbidity status, American Society of Anesthesiologists classification, laboratory data, imaging results, surgical procedures, postoperative complications, and postoperative length of stay of the patients were analyzed.* ***Results:*** *There were 46 (9.6%) patients with the diagnosis of gallbladder perforation. Morbidity and mortality occurred in 15 (32.6%) and 7 (15.2%) patients, respectively. Advanced age, male gender, fever >38°C, high white blood cell count, and presence of cardiovascular comorbidity were found to be significant risk factors for gallbladder perforation.* ***Conclusions:*** *While early diagnosis and early surgical intervention are the keys to managing gallbladder perforation, we suggest that patients having the above-mentioned clinical features should be carefully investigated.*

Key words: Acute cholecystitis, gallbladder perforation, surgery

Safra kesesi perforasyonları: 46 hastanın klinik özellikleri, predispozan faktörleri ve cerrahi sonuçları

Amaç: *Bu çalışmada safra kesesi perforasyonu gelişen olguların klinik özellikleri, perforasyon tipleri arasındaki farklılıkları ve perforasyona etki eden risk faktörleri incelemek amaçlanmıştır.* ***Yöntem:*** *Kliniklerimizde Ocak 1997-Kasım 2008 tarihleri arasında akut kolesistit nedeniyle acil cerrahi girişim uygulanan 478 olgu retrospektif olarak incelendi. Olguların demografik özellikleri, semptom süresi, yandaş hastalıklar, ASA skorlaması, labaratuvar değerleri, tanısal yöntemler, intraoperatif bulgular, cerrahi işlemler, postoperatif komplikasyonlar ve hastanede kalış süresi incelendi.* ***Bulgular:*** *Olguların 46'sı (%9.6) safra kesesi perforasyonu tanısı aldı. Morbidite ve mortalite sırasıyla 15 (%32.6) ve 7 (%15.2) olguda görüldü. İleri yaş, erkek cinsiyet, 38°C üstündeki ateş, lökositoz ve kardiovasküler sistem yandaş hastalığı risk faktörleri olarak bulundu.* ***Sonuç:*** *Risk faktörlerine sahip olguların daha dikkatli değerlendirilmesi gerektiğini, erken tanı ve tedavi ile morbidite ve mortalitenin azalacağına inanıyoruz.*

Anahtar kelimeler: Akut kolesistit, safra kesesi perforasyonu, Cerrahi

INTRODUCTION

Gallbladder perforation (GBP) is a rare but life-threatening complication of acute cholecystitis. It has been reported to occur in 2-15% of patients with acute cholecystitis, and is usually associated with the presence of stones. GBP sometimes may not differ from uncomplicated acute cholecystitis resulting in high morbidity and mortality rates because of delay in diagnosis (1-3). A number of im-

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provements have been made in the recognition and management of this complication in the last two decades, leading to a decrease in the mortality (4). Nevertheless, most cases can only be diagnosed intraoperatively, so this continues to be an important problem for surgeons (1,2,5).

Niemeier (6), in 1934, classified GBP as acute or type I for free perforation and generalized biliary peritonitis, subacute or type II for pericholecystic abscess and localized peritonitis, and chronic or type III for cholecystenteric fistula. This classification is still in use. It is important to realize that the three types of perforation have different presentations. Patients with type I perforation usually have risk factors leading to immunodeficiency that prevents localization of the inflammation, thus leading to free perforation and generalized peritonitis. Patients with type II perforations present with features not typical of acute cholecystitis, and type III patients present with features similar to those of chronic cholecystitis and so are difficult to identify preoperatively unless they have obstructive symptoms (3,5). The relation between patient characteristics and their clinical features and the type of GBP has not been defined in the literature before.

Various prognostic factors have been proposed as risk factors that contribute to the development of complications, such as gangrene, empyema, emphysematous cholecystitis, and perforation, in patients with acute cholecystitis. Advanced age, male sex, associated diseases, fever >38°C, and marked leukocytosis should prompt an increased awareness for complications (7-9). However, there is no study in the literature that investigates predisposing factors in patients with acute cholecystitis that contribute to the development of perforation, using logistic regression analysis.

In this study, we report our experience with the aims of describing the clinical features of this entity and the relation between patient characteristics and the different types of GBP and determining the predisposing factors.

MATERIALS AND METHODS

The medical records of 478 patients who received urgent surgical treatment at the time of admission with the diagnosis of acute cholecystitis and patients who developed complications during conservative follow-up of acute cholecystitis and underwent urgent surgery in our clinics between January 1997 and November 2008 were reviewed retrospectively. Forty-six (9.6%) of those patients were found to have GBP. The diagnosis of GBP was based on operative findings. Three hundred and two patients with acute cholecystitis, who received medical treatment and were operated on an elective basis, were excluded from this study. In addition, perforations due to trauma, iatrogenic causes and gallbladder carcinoma were not included in this study. The original classification of Niemeier (6) was used to identify the patients.

The diagnosis of acute cholecystitis was made by the presence of positive abdominal findings (right upper quadrant tenderness, guarding, positive Murphy sign, localized rebound, rigidity), leukocytosis, fever, and ultrasonographic findings like thickened gallbladder wall and/or pericholecystic fluid. If the above-mentioned criteria were present at the time of admission and the general physical condition of the patients allowed the procedure, immediate surgery was performed within the first 72 hours after administration of intravenous crystalloid solutions, analgesics and antibiotic (third-generation cephalosporins) treatment. The patients who had associated diseases such as diabetes or cardiac and pulmonary disease underwent surgery after specific medical treatment had been started. The demographic data of patients, time elapsed from the onset of the symptoms to the time of surgery, comorbidity status (cardiovascular disease, diabetes mellitus, and others [chronic obstructive pulmonary disease, immunosuppressive diseases or immunosuppressive treatment]), American Society of Anesthesiologists (ASA) classification, laboratory data (routine blood count, blood chemistry tests), imaging results (abdominal ultrasound (US) scan, abdominal contrast enhanced computerized tomography (CT), direct chest and abdominal X-ray series), surgical procedures, postoperative complications, and postoperative length of stay (LOS) of the patients were analyzed.

Statistical Analysis

Differences among categorical variables were compared using the chi-square test, the Mann-Whitney U test and ANOVA test. Univariate and multiple logistic regression analyses were performed to analyze the effects of variables that influenced GBP. Data were analyzed with the SPSS software package (SPSS; 11.5; Standard Version, Chicago, IL, USA). A P value <0.05 was considered significant.

RESULTS

Demographic and Clinical Profiles

A comparison of the mean age between patients with GBP and those with acute cholecystitis without perforation revealed that the mean age was significantly higher in the GBP group (68.45 ± 7.85 vs. 62.08 ± 9.14 years, p<0.01). The mean age of the type III patients was higher than of the type I and type II patients, and there was a significant difference in the mean age between patients with type III and type I (p<0.05). There were 29 (63.0%) male and 17 (37.0%) female patients. The male:female ratio in the GBP group was 1.7:1 compared to a ratio of 0.8:1 in the group without perforation, and there was a significant difference between the two groups (p=0.020). A greater proportion of patients with types I and II perforations were men, but these differences were not statistically significant in groups (p>0.05). Fever was noted in 80.4% patients in the perforation group and in 56.3% in the group without GBP (p<0.01). Fever >38°C in patients with types I and II was significantly higher than in the type III patients (p<0.05). There was significant difference between GBP patients and patients without perforation with respect to leukocytosis (mean 18.656 ± 8.808 vs. 14.767±3.661, p<0.01). The mean white blood cell (WBC) count of the type I patients was superior to the other groups, but the difference was not statistically significant (p>0.05). There was a significant difference between the GBP and without perforation groups in terms of mean duration of symptoms (p<0.01) and history of cholelithiasis (p=0.009). Duration of symptoms with type I and II patients and history of cholelithiasis with type I patients were statistically significantly shorter than among the type III patients (p<0.05). The average operating time and LOS were also significantly longer for the perforation group (132±40.5 vs. 96±26.7 minutes, p<0.01; and 11.15±4.25 vs. 9.36±2.91 days, p<0.01, respectively). Patients with type III perforation had a longer operating time than types I and II patients (164.8±33.9 vs. 129.7±43.6 and 121.4±34.7 minutes (min) respectively, p<0.05). The average LOS of Group II was significantly shorter in comparison with Group I (8.8±3.5 vs. 13.6±4.5 days, respectively). The frequency of cardiovascular comorbidity in the perforated cholecystitis group was significantly higher than in the nonperforated group (p=0.001). In contrast, diabetes comorbidity (p=0.866) and ASA scores (p=0.291) were similar in the patients with GBP and those without perforation. Cardiovascular comorbidity was more commonly detected in the types I and II patients than in type III patients, while diabetes was more commonly encountered in the patients with types II and III (p<0.05). The incidence of morbidity and mortality in patients with GBP was higher than in patients without perforation (p=0.022 and p=0.006, respectively). Patients with type I perforation had a higher morbidity and mortality rate compared to those with types II and III perforation, but these differences were not statistically significant (p>0.05). Comparative data between patients with GBP and no perforation are listed in Table 1. Patient characteristics and differences between the different types of perforations are shown in Table 2.

In the univariate analysis of factors that influence perforation of the gallbladder, advanced age, male gender, fever >38°C, high WBC count, and presence of cardiovascular comorbidity were found to be significant risk factors. All these parameters were also found as predisposing factors for GBP in the multiple logistic regression analysis (Table 3).

Diagnostic Evaluation

Chest and abdominal radiography and abdominal US were performed in all patients at admission. Abdominal US did not show gallbladder wall defect in any of the cases, but it was helpful in suspecting a perforation (extensive intraperitoneal free fluid, pericholecystic collection with a thickened gallbladder wall) in 25 (65.8%) of the 38 patients with type I and II perforations. Abdominal CT was performed in 35 (76.1%) patients, and it confirmed US findings and revealed the perforation site on the gallbladder in 5 (14.3%) of the patients, so the diagnosis of GBP was made correctly preoperatively in only 5 patients. Abdominal US and CT were reported as dilated intestinal loops suggesting mechanical obstruction in all of 8 patients with type III perforation. Perforations were confirmed intraoperatively in all 46 patients.

Surgery

The median interval time from admission to surgery was 8.1 hours (range: 1–124 hours). A total of 40 patients were operated within 72 hours (range: 1-72 hours), while the remaining 6 patients underwent surgery more than 72 hours after presentation (range: 72-124 hours) because of associated disease that required stabilization. During surgery, types I, II, and III perforations were found in 17 (36.9%), 21 (45.7%), and 8 (17.4%) patients, res-

Table 1. Patient characteristics of the two groups

Patient characteristics	Gallbladder perforation *(n=46)*	Acute cholecystitis without perforation *(n=432)*	*P*
Age (years) (Mean ± SD)	68.45±7.85	62.08±9.14	<0.01
Sex			
Male	29 (63.0%)	195 (45.1%)	0.020
Female	17 (37.0%)	237 (54.9%)	
Fever ≥38°C			
No	9 (19.6%)	189 (43.7%)	<0.01
Yes	37 (80.4%)	243 (56.3%)	
WBC count (mean)	18.656	14.767	<0.01
Mean duration of symptoms (days)	9.71	7.66	<0.01
History of cholelithiasis (months)	7.08	6.21	0.009
Comorbid conditions			
Cardiovascular	29 (63.0%)	165 (38.2%)	0.001
Diabetes	19 (41.3%)	184 (42.6%)	0.866
Others	6 (13.0%)	36 (8.3%)	0.205
ASA scores			
I-II	12 (26.1%)	146 (33.8%)	0.291
III-IV	34 (73.9%)	286 (66.2%)	
Operating time (min)	132.0	96.0	<0.01
LOS (days)	11.15	9.36	<0.01
Morbidity			
Positive	15 (32.6%)	80 (18.5%)	0.022
Negative	31 (67.4%)	352 (81.5%)	
Mortality			
Positive	7 (15.2%)	22 (5.1%)	0.006
Negative	39 (84.8%)	410 (94.9%)	

pectively. The most common site of perforation was the fundus, in 50.0% of cases.

All of patients with type I perforation underwent cholecystectomy. Peritoneal spaces were lavaged thoroughly with isotonic saline, and drains were placed for postoperative drainage. Three of the 21 patients with type II perforation were managed conservatively with a diagnosis of acute cholecystitis, developed complications during follow-up, and underwent urgent cholecystectomy and drainage. Two patients underwent surgery more than 72 hours after presentation because of associated disease that required stabilization. One patient with type II perforation underwent percutaneous drainage of the collection in the pericholecystic region under US guidance. All the other type II patients received urgent cholecystectomy and drainage. In the type III perforation group, all of 8 patients with gastrointestinal tract obstruction underwent laparotomy after initial fluid resuscitation. The gallstone was removed through an enterotomy and cholecystectomy was added.

Laparoscopic cholecystectomy was performed in 13 patients. Four of them were type I and 9 were type II perforation. Conversion was required in 8 of them due to intense inflammation and unclear anatomy. Conventional cholecystectomy was attempted in all patients with type III.

Morbidity and Mortality

A total of 21 morbidities developed in 15 patients (32.6%). Major complications included subhepatic abscess (n=3), pelvic abscess (n=3), pneumonia (n=3), postoperative ileus (n=1), anastomotic leakage (n=1), wound dehiscence (n=1), acute pancreatitis (n=1), acute renal failure (n=1), and myocardial infarction (n=1), while minor complications included local wound infection (n=4) and urinary infection (n=2). Except for 1 patient with anastomotic leakage, all the other morbidities were treated conservatively. Subhepatic and pelvic abscesses were drained percutaneously under US guidance. Wound infections were successfully managed with drainage and local wound care. Seven patients (15.2%) died because of sepsis and multiple organ failure in the early postoperative period.

Table 2. Patient characteristics and sites of perforation in each group of perforation types

Patient characteristics	Type I (n=17)	Type II (n=21)	Type III (n=8)
Mean age (years)	65.6±5.6	68.8±9.4	73.5±4.3*
Gender			
Male	11 (64.7%)	14 (66.7%)	4 (50.0%)
Female	6 (35.3%)	7 (33.3%)	4 (50.0%)
Fever ≥38°C	17 (100.0%)¶	18 (85.7%)¶	2 (25.0%)
White blood cell count (median)	19700	17600	15500
Mean duration of symptoms (days)	5.8 ¶	8.7 ¶	20.5
History of cholelithiasis (months)	1.0 ¶	9.5	13.5
Comorbid conditions			
Cardiovascular	12 (70.6%)¶	14 (66.6%)¶	3 (37.5%)
Diabetes	6 (35.3%)	12 (57.1%)*	6 (75.0%)*
Others	3 (17.6%)	2 (9.5%)	1 (12.5%)
Cholecystectomy			
Laparoscopic	4 (23.5%)¶	9 (42.9%)¶	-
Conventional	13 (76.5%)	12 (57.1%)	8 (100.0%)
The sites of perforation			
Fundus	13 (76.5%)¶	10 (47.6%)¶	-
Corpus	3 (17.6%)	6 (28.6%)	2 (25.0%)
Infundibulum and cystic duct	1 (5.9%)	5 (23.8%)*	6 (75.0%)*
Operating time (min)	129.7¶	121.4¶	164.8
LOS (days)	13.6	8.8 *	12.0
Morbidity			
Positive	7 (41.2%)	7 (33.3%)	1 (12.5%)
Negative	10 (58.8%)	14 (66.7%)	7 (87.5%)
Mortality			
Positive	4 (23.5%)	2 (9.5%)	1 (12.5%)
Negative	13 (76.5%)	19 (90.5%)	7 (87.5%)

* P<0.05 compared with type I. ¶ P<0.05 compared with type III.

Table 3. Univariate and multiple logistic regression analyses of factors influencing perforation of gallbladder

Patient characteristics	Univariate logistic regression	Multiple logistic regression analysis		
	P	Odds ratio	95% CI	P
Age (years) ≥65	<0.01	4.0	1.92-8.55	<0.01
Gender (Male/Female)	0.001	3.50	1.63-7.50	0.001
Fever ≥38°C	0.007	0.31	0.14-0.69	0.005
White blood cell count ≥15000	<0.01	7.38	3.15-17.26	<0.01
Mean duration of symptoms (days)	0.072			
History of cholelithiasis (months)	0.142			
Comorbid conditions				
Cardiovascular	0.006	2.72	1.36-5.45	0.005
Diabetes	0.959			
Others	0.759			
ASA scores (III-IV)	0.552			

CI: Confidence interval.

DISCUSSION

Perforation of the gallbladder (GBP) is an important complication of acute cholecystitis. It is not possible to predict reliably in which patients this complication will develop (3,5,7,10). Strohl et al. (11) reported the results of a series involving 31 patients with perforation whose symptoms were similar to those in patients with uncomplicated

acute cholecystitis. Acute uncomplicated cholecystitis is more common among females, with a female to male ratio of two to one (12); however, GBP is more frequent in the male gender (1,2,5,7). Sixty-three percent of our cases were males. Roslyn et al. (1) reported that there were a greater number of men than women with type I and type II perforations, as compared to those with type II-I perforations. In our study, patients with type I and type II perforations tended to have a higher incidence of male gender compared to patients with type III perforations, but these differences failed to achieve statistical significance. We found that the disease occurs more frequently in elderly patients, and the cases with type III perforation were older than those in the type I and II groups, which is in accordance with other reports (4,13).

The predictive value of clinical findings or laboratory tests in the diagnosis of acute cholecystitis has been questioned in a systematic literature review (14). Parker et al. (15) reported that high fever, right upper quadrant pain, and elevated WBC count are not diagnostic features for GBP. The authors found high fever in 56% and high WBC count in 59% of the cases with acute cholecystitis. As has been suggested by other investigators (7,9,16), our study revealed that high fever and leukocytosis were associated with a higher incidence of perforation. The majority of type I and II cases had fever, whereas type III cases did not in our study. The cases with type I and II perforation had elevated WBC count, but those with type III perforation had only a mild increase in WBC count, and the difference was not statistically significant between the groups.

Bedirli et al. (7) reported that the interval between the onset of symptoms and operation was significantly longer in patients with GBP than in those without perforation. The duration of symptoms was shortest for patients with type I perforation and increased for type II and for type III patients, and most of patients in this study with type III perforations had a previous long history of gallstone disease, as has been reported in other articles (1,3,17). Type I perforations occur more commonly in patients without a history of chronic gallstone disease who have a serious associated systemic disease (1,13,18). Some systemic diseases, such as atherosclerotic heart disease and diabetes, may induce ischemia of the gallbladder wall, leading to necrosis and perforation (1-5). Stefanidis et al. (2) reported that cardiovascular comorbidity appears to be a risk factor for perforation, with half of the patients with perforation affected by it. In our study, cardiovascular comorbidity was more commonly detected in the patients with GBP than in the nonperforated group, and there was no difference in the incidence of diabetes between the two groups.

Gallbladder perforation (GBP) is rarely diagnosed preoperatively. In one review, a correct diagnosis was established preoperatively in only one of the nine (11.1%) patients (19). US could not specifically identify perforations, but it was helpful in determining the need for surgical intervention, as it could identify the presence of pericholecystic free fluid (3,5). Sood et al. (10) noted that the sonographic hole sign, in which the defect in the gallbladder wall is visualized, is the only reliable sign of GBP. However, in Kim et al.'s study (20), the site of the defect was not visualized by US in any of the 13 patients. Similarly, none of the patients was reported as showing perforated gallbladder in the ultrasonographic examination in our study. CT scan appears to improve the diagnostic accuracy. CT with thin slices can also show gallbladder wall thickness, and the defect on the wall due to perforation (10,21). All of the five (14.3%) patients with the diagnosis of GBP preoperatively were diagnosed by CT. Since the cases were admitted to the hospital with acute abdominal pain, standard abdominopelvic CT, not thin slice upper abdominal CT, was applied. There are studies on Doppler ultrasound, magnetic resonance imaging and radionuclide methods used in GBP reporting good results. However, the use of all of these methods is not very common or practical (22,23).

In this study, the incidence of GBP was 9.6% among cholecystectomized patients, and the diagnosis of GBP was based on operative findings. The incidence of type II GBP was more frequent (45.7%), and the most frequent site of perforation was the fundus (50%) in our study, which is similar to other reports in the literature (1,3,17). The infundibulum/cystic duct was the most common site of perforation of cases with types II and III perforations in this study. We previously reported that when the gallbladder is perforated at the fundus, the omentum possibly covers the gallbladder less; thus, the bile drains into the peritoneal space. If the perforation is not at the fundus, it is easily sealed by the omentum or the intestines and the condition remains limited in the right upper quadrant, with formation of a plastron and peric-

holecystic fluid. This observation suggests that if the perforation is at the fundus, it is more likely to result in a type I perforation (5).

We perform urgent cholecystectomy in the patients with acute cholecystitis in the first 72 hours after the diagnosis if they are stable. Urgent cholecystectomy for patients with acute cholecystitis is safe, cost-effective, and leads to less time off work compared with delayed surgery (2,7). Cholecystectomy, drainage of the abscess, if present, and abdominal lavage are usually sufficient to treat GBP (1,4). Percutaneous cholecystostomy by US or CT is gaining acceptance as an alternative to the surgical procedure in clinically critical patients (3,24). Laparoscopic cholecystectomy can be performed for the acute, gangrenous and perforated cholecystitis, but it is still very difficult, and a conversion may be necessary in case of difficulties like an unclear anatomy (2,3,25). In our study, laparoscopic procedure was initiated in 13 patients but conversion was required in eight (61.5%).

The frequency of postoperative morbidity, mortality and postoperative hospital stay increased when perforation was present (2,7). Morbidity and mortality rates in the perforated cholecystitis group were significantly higher than in the nonperforated group (p=0.022 and p=0.006, respectively), but these rates were not different between the three types of GBP, in our study. Glenn and Moore (26), about half a century ago, reported the mortality rate as 42%. Mortality rates decreased to 7-16% in the following years owing to the developments in anesthesiology and intensive care conditions (2,3). Morbidity and mortality rates were 32.6% and 15.2%, respectively, in this study.

Multivariate analyses must be employed in order to evaluate the relations between variables that affect complications and to identify independent risk factors. Older age, male gender, fever >38°C, high WBC count, and presence of cardiovascular disease were important predisposing factors in the multiple logistic regression analysis. To our knowledge, ours is the first study to investigate factors that affect perforation in acute cholecystitis patients using multivariate analyses. Furthermore, this is the first study to define the relation between patient characteristics, their clinical features and the different types of GBP.

In conclusion, the diagnosis of GBP is rarely made before operative exploration. It can be made preoperatively with a high degree of suspicion of the condition aided by imaging findings. In any elderly male patient with symptoms of acute cholecystitis who has predisposing factors, perforation should be suspected. While early diagnosis and early surgical intervention are the keys to managing GBP, we suggest that in patients having these clinical features, early surgery should be performed.

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