GALL BLADDER PERFORATION: A CASE-SERIES & PROPOSAL OF THE ALGORITHM TO A MANAGEMENT PLAN

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ABSTRACT Introduction: Gallbladder perforation (GBP) is a rare & life-threatening complication of both benign & malignant diseases of the gall bladder which requires aggressive supportive management and sepsis control in the initial phase. Followed by further evaluation to know the pathology of GBP and definitive surgical management. Hence, this study aims to describe an algorithmic approach based on our case series. **Material and Methods:** A retrospective study of GBP patients between 2016 and 2020 in a tertiary care centre. Comparisons were made between xanthogranulomatous cholecystitis (XGC) vs. chronic cholecystitis (CC) & benign vs. malignant disease. **Results:** 81 patients with GBP were included. The mean age was 54 years. Male: Female ratio was 1.13. Mortality was 3.7% (n=3). The most common clinical presentation was a combination of pain in the right upper quadrant of the abdomen & fever with chills or rigours in 61(75.3%) cases. Surgery was performed in 62 patients (76.5%), and open cholecystectomy 23 (37.7%) was the most common. 7 had the malignant disease in the final histopathology. The most common aetiology was XGC – 32 (51.61%). **Conclusions:** GBP is a complex problem, requiring aggressive multidisciplinary management in the initial phase, followed by meticulous evaluation before definitive surgery.

KEYWORDS Gall bladder perforation, Xanthogranulomatous cholecystitis, Chronic cholecystitis, Subtotal cholecystectomy, Carcinoma gall bladder,

Introduction

Acute cholecystitis, either calculus or acalculous, can lead to spontaneous gall bladder perforation (GBP), a rare clinical entity associated with increased morbidity and mortality. A mortality rate of 12 - 42% has been reported. [1-3] In 1934, Neimeier classified GBP and brought uniformity in reporting.[4] He classified GBP into 3 types, namely acute perforation into the free peritoneal cavity (Type I), subacute perforation with abscess formation (Type II) & chronic perforation with internal fistula (Type III). Since then, several investigators have modified or sub-classified type III GBP. [5, 6] GBP can lead to acute biliary peritonitis, sepsis, septic shock, MODS (multiple organ dysfunction syndromes) and mortality, which requires aggressive multi-disciplinary management. Despite the evolution in the management of GBP, the pathophysiology remains elusive. Increased intraluminal pressure in the gallbladder (GB) leading to necrosis of the wall due to vascular compromise as the cystic artery is an end artery or a combination of increased pressure with decreased wall strength due to inflammation has been proposed. Patient's co-morbidities, along with the underlying disease process, either xanthogranulomatous cholecystitis (XGC), chronic cholecystitis (CC) or gall bladder carcinoma (GBC), can further complicate the evaluation and management. Here we propose an easy-to-use algorithmic approach to manage this complex clinical condition based on a 5 years case series.

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Methods

This was a retrospective analysis of our electronic database of GBP patients admitted to our tertiary care referral centre between January 2016 and December 2020. Patients presenting with GBP were evaluated for hemodynamic status, sepsis, intra- abdominal collection, co-morbidities & possible underlying aetiology. The diagnosis of GBP was made based on clinical features, laboratory investigations and imaging investigations (USG/CT/MRI abdomen) Figure 1. They were managed according to the algorithm shown in Figure 2. After initial management with antibiotics ± percutaneous cholecystostomy (PCC) &/or percutaneous drainage (PCD), patients were planned for an elective total/ sub-total cholecystectomy either by laparoscopic or open approach. Those patients suspected to have dense adhesions due to previous pericholecystic collection, which precluded safe cholecystectomy underwent subtotal cholecystectomy as it was a safe recourse & could be performed laparoscopically Figure 3.[7] Thick-walled gall bladder (wall thickness >3mm) poses a diagnostic challenge, which has to be evaluated with a contrast-enhanced computed tomography (CECT) scan, Magnetic Resonance Imaging (MRI) scan with diffusion-weighted imaging (DWI) &/or PET-CT scan to rule out malignancy.[8] In case of suspicion of GBC, staging laparoscopy followed by extended cholecystectomy was performed and managed according to the stage of the disease. Demographic profiles, clinical presentation, investigations, initial treatment, definitive surgery, postoperative course & histopathology were recorded in a proforma and tabulated in MS Excel. It was a retrospective analysis of a prospective database, so no ethical clearance was sought. All participants signed the "informed consent form".

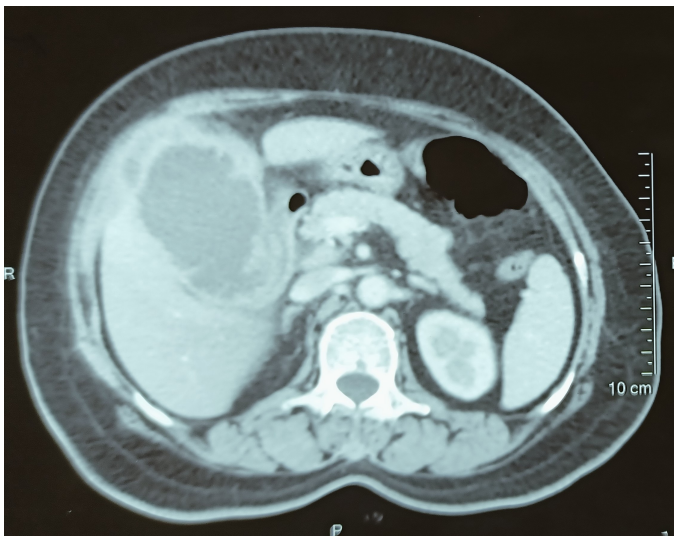

Figure 1 CT axial image of the abdomen showing diffuse thickening of the gall bladder with pericholecystic fluid collection; (contained gallbladder perforation).

Statistical Analysis

The comparison was made among patients with XGC vs. CC and benign vs malignant disease. Continuous variables were recorded as mean ± standard deviation and categorical variables as a percentage (%). Independent t-test and chi-square tests were applied using SPSS - 22, and a p-value of < 0.05 was considered statistically significant.

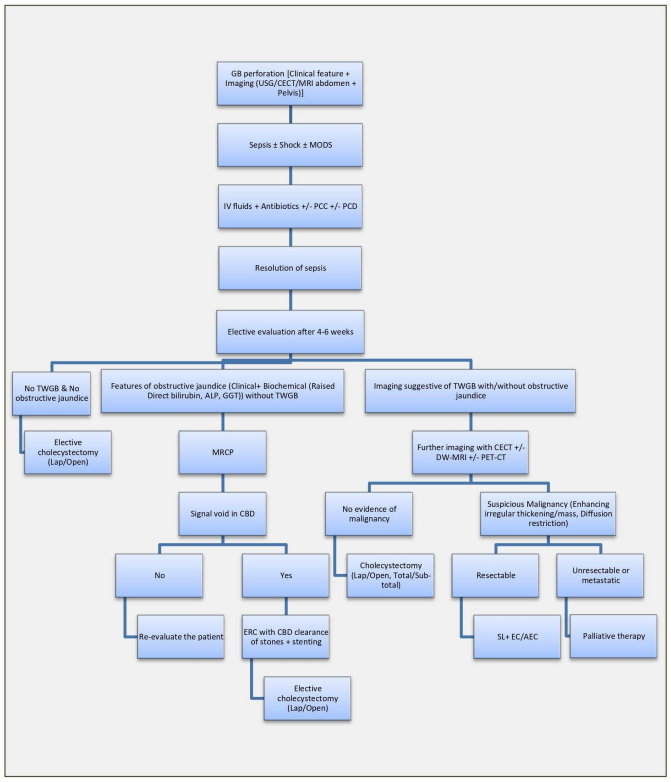

Figure 2 Proposed algorithm for the management of Gall bladder perforation. **ALP** - Alkaline Phosphatase; **CBD** - Common Bile Duct; **EC** - Extended Cholecystectomy; **GGT** - Gamma Glutamyl Transpeptidase; **MRCP** - Magnetic Resonance Cholangio Pancreatogram; **PCC** - Percutaneous Cholecystostomy; **PCD** - Percutaneous Drainage; **TWGB** - Thick-Walled Gall Bladder; **SL** - Staging Laparoscopy.

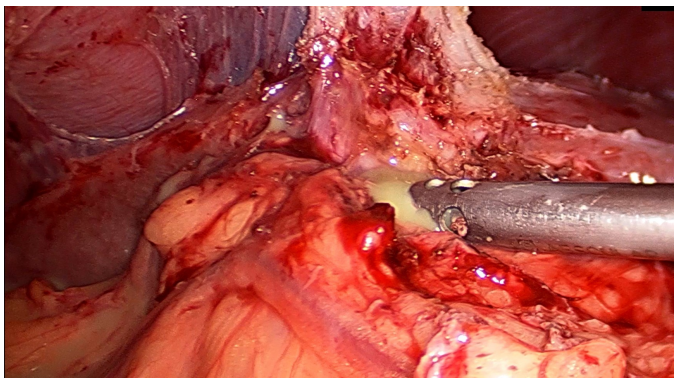

Figure 3 Intraoperative image of laparoscopic cholecystectomy in case of gall bladder perforation.

Results

The medical records of 2189 acute or chronic cholecystitis cases were retrospectively reviewed, between January 2016 and December 2020, where 81 patients were diagnosed with gall bladder perforation. Their mean age was 54 years. The majority were male patients (M=43, F=38). Niemeier type II GBP was the most common (85.1%, n=69). The most common presentation was a combination of abdominal pain, fever and chills/rigour (n=61, 75.3%). In the initial phase, most patients were managed

Table 1 Demographic profile of patients.

Parameters (n=81)	***Value***
Age (in years), Mean ± SD	*54±15.6*
Gender (M/F)	*43/38*
Co-morbidity, n (%)	*38 (46.9)*
Diabetes mellitus, n (%)	*14(17.2)*
Hypertension, n (%)	*13 (16)*
Coronary artery disease, n (%)	*8 (9.8)*
Multiple co-morbidities, n (%)	*10 (12.3)*
Type of perforation	
Type-I, n (%)	*11 (13.5)*
Type-II, n (%)	*69 (85.1)*
Type-III, n (%)	*1 (1.2)*
Organ failure on presentation, n (%)	*3 (3.7)*
Benign/ Malignant (among operated patients), n	*55/7*
Xanthogranulomatous cholecystitis, n (%) (among operated patients)	*32(51.61)*
Chronic cholecystitis (among operated patients)	*23(37.09)*
Adenocarcinoma, n (%) (among operated patients)	*7 (11.29)*
Associated with cholelithiasis, n (%) of all 81 cases	*63 (77.7)*
Presentation	
Abdominal pain + fever + chills/rigor, n (%)	*61 (75.3)*
Vomiting, n (%)	*32 (39.5)*
Pain abdomen, n (%)	*26 (32)*
Abdominal distension, n (%)	*6 (7.4)*
Jaundice, n (%)	*7 (8.6)*
Anorexia/ weight loss, n (%)	*3 (3.7)*
Pruritus, n (%)	*3 (3.7)*
Loose stools, n (%)	*1 (1.2)*
Management	
Antibiotics alone, n (%)	*18 (22.22)*
Antibiotics + PCD, n (%)	*15 (18.5)*
Antibiotics + PCC, n (%)	*34 (41.9)*
Antibiotics + PCD + PCC, n (%)	*13 (16.0)*
Antibiotics + Single time aspiration n (%)	*1 (1.2)*
Definitive surgery (n=62)76.54%	
AEC, n (%)	*3(4.8)*
Extended cholecystectomy, n (%)	*3 (4.8)*
Laparoscopic cholecystectomy, n (%)	*16 (25.8)*
Laparoscopic converted to open subtotal cholecystectomy, n (%)	*4 (6.4)*
Laparoscopic converted to open cholecystectomy, n (%)	*1 (1.6)*
Laparoscopic subtotal cholecystectomy, n (%)	*8 (12.9)*
Open cholecystectomy, n (%)	*23 (37.0)*
Open subtotal cholecystectomy, n (%)	*4 (6.4)*
No surgery, n (%)	*19 (23.4)*

AEC - Anticipatory Extended Cholecystectomy; PCC - Percutaneous Cholecystostomy; PCD - Percutaneous Catheter Drainage; SD - Standard Deviation.

Table 2 Comparison between Xanthogranulomatous cholecystitis (XGC) and Chronic cholecystitis (CC) (Documented on Histopathology).

Parameters	*XGC (n=32)*	*No XGC(CC) (n=23)*	*p-value*
Age (in years), Mean ± SD	*52.28±12.58*	*50.95±15.1*	*0.24*
Sex (M/F), n	*19/21*	*11/12*	*0.582*
Co-morbidities, n (%)	*10 (31)*	*12(54.5)*	*0.101*
Diabetes mellitus, n (%)	*1(3.2)*	*5(22.7)*	*0.036*
Hypertension, n (%)	*3 (9.6)*	*5(22.7)*	*0.248*
Coronary artery disease, n (%)	*6 (19.3)*	*0*	*0.071*
Multiple co-morbidities, n (%)	*4 (12.9)*	*3 (13.6)*	*1*
Type of perforation, n			*0.211*
Type I	*2*	*4*	
Type II	*30*	*25*	
Type III	*0*	*1*	
Presentation, n (%)			
Pain + fever + chills/rigor	*22 (70.9)*	*17 (77.27)*	*0.439*
Vomiting	*10 (31.25)*	*11 (50)*	*0.256*
Abdominal distension	*2 (6.25)*	*1 (4.5)*	*1*
Jaundice	*4 (12.50)*	*3 (13.04)*	*1*
Pruritus	*0*	*1 (4.5)*	*0.407*
Pain abdomen alone	*11 (34.3)*	*4 (18.2)*	*0.811*
Anorexia/ weight loss	*1 (3.12)*	*2 (9)*	*0.560*

SD - Standard Deviation.

Table 3 Comparison between malignant and benign conditions.

Parameters	*Malignant (n=7)*	*Benign (n=*
Age (in years), Mean ± SD	*62±13.7*	*51.2±13.5*
Sex (M/F), n	*3/4*	*30/25*
Co-morbidities, n (%)	*2 (28.5)*	*22 (40.7)*
Diabetes mellitus, n (%)	*2 (28.5)*	*6 (11.1)*
Hypertension, n (%)	*1 (14.25)*	*8 (14.8)*
Coronary artery disease, n (%)	*0*	*6 (11.1)*
Multiple co-morbidities, n (%)	*0*	*7(12.7)*
Type of perforation, n		
Type I	*0*	*7*
Type II	*7*	*48*
Type III	*0*	*0*
Presentation, n (%)		
Pain + fever + chills/rigor	*4 (57.14)*	*39 (72.2)*
Vomiting	*1 (14.2)*	*21 (38.8)*
Abdominal distension	*1 (14.2)*	*3 (5.55)*
Jaundice	*1 (14.2)*	*5 (9.25)*
Pruritus	*1 (14.2)*	*1 (1.85)*
Pain abdomen alone	*2 (28.4)*	*15 (27.7)*
Anorexia/ weight loss	*0*	*3 (5.55)*

SD - Standard Deviation; NA - Not Applicable

Table 4 Various studies on gall bladder perforation.

Serial number	Author/ Year of study	Sample size (n)	Mean Age (years)	Male (%)	Neimeier classification of gall bladder perforation (%)			Cholelithiasis (%)	Mortality (%)
					I	II	III		
1	Menakuru,12 2004	31	68	38.7	29	45.1	26	93.5	9.7
2	Derici,1 2006	16	70	62.5	44.8	44.8	12.5	-	12.5
3	Stefanidis,18 2006	30	60	76.7	70	30	0	-	-
4	Ergul,19 2008	37	64	54.1	32.4	56.8	10.8	89.2	10.8
5	H Derici,20 2011	46	68	63	36.9	45.6	17.3	-	15.2
6	Date RS,9 2012	19	72	52.6	47.4	47.4	5.3	78.9	0
7	Gunasekaran G,21 2015	32	56	40.6	43.7	37.5	18.7	-	15.6
8	NA Sahbaz,22 2017	133	64	66.6	49.6	39.1	11.3	-	10.5
9	Present study, 2022	81	54	53.0	13.5	85.1	1.2	77.7	3.7

with antibiotics, percutaneous cholecystostomy &/or percutaneous drainage. Open cholecystectomy was the most commonly performed surgical procedure (37.7%, n=23). XGC was the most common pathology (51.61%, n=32); adenocarcinoma was seen in 7 (11.29%) patients. The demographic profile of GBP patients is shown in Table 1. CC was associated with more co-morbidity compared to XGC (54.5% vs 31.0%). Diabetes mellitus, the most common co-morbidity, was also more commonly associated with CC (CC - 22.7% vs XGC - 3.2%, p - 0.03). The rest of the parameters were comparable, as shown in Table 2. Though not statistically significant, malignancy was more common among the aged 62 years vs 51 years in benign disease (p - 0.84) & co-morbidities were more common among those with benign diseases 40.7% vs 28.5% in malignancy (p - 0.23) table 3 shows the detailed comparison. Discussion: GBP was first officially reported by Duncan in 1844. Niemeier, in 1934, proposed a classification system for GBP. With the development and evolution of medical imaging technology & experience in managing GBP, various investigators have proposed additions and modifications to the original Neimeier classification. GBP can present in myriad ways. A patient can either be present with mild to moderate symptoms of abdominal pain and fever or features of sepsis &/or organ failure. It can sometimes cause fulminant sepsis leading to mortality. So, it is an emergency requiring multidisciplinary management involving a surgeon, an interventional radiologist, a gastroenterologist & a critical care specialist. After initial resuscitation & control of sepsis, further evaluation is very important, as there may be an underlying malignancy lurking beneath the inflammation, based on which further treatment will be planned.

In a study by Date RS et al., 31.6% of patients had a co-morbid illness. [9] The most common site of GBP was the fundus because of its poor blood supply. [10-12] Secondly, acute cholecystitis can progress to cause ischemia, necrosis and consequent perforation. [13, 14]

Rarely, it may also result from acalculous cholecystitis. [16] Studies have reported varied incidences of a type of GBP, as shown in Table 4. GBP is commonly seen in the elderly age group (47 to 72 years - table 4). However, in our study, the mean age was 54 years. Most studies reported male preponderance, but our study showed almost equal gender distribution with slight male preponderance. Most patients had co-morbidities, with diabetes mellitus being the most common. Type II GBP was the most common in our study, followed by type I. Mortality was 3.7% (n=3) during the initial treatment phase, which varied from 0% - 15.2% in the searched literature, as shown in Table 4. The most common clinical presentation was pain in the right upper quadrant of the abdomen & fever with chills or rigours (75.3%). Seven patients presented with jaundice (choledocholithiasis - 5, sepsis-induced - 1, benign CBD stricture – 1. Among choledocholithiasis patients diagnosed during pre-operative imaging, 1 patient required CBD exploration along with cholecystectomy, 1 patient succumbed to cholangitis and multiorgan failure, and the remaining 3 patients underwent cholecystectomy after endoscopic stone clearance. In the initial phase, all patients were resuscitated with IV fluids & antibiotics. In addition to this, 3.8% (n=3) needed organ support. Only a PCC tube was inserted when there was a GBP with GB still distended & no significant pericholecystic collection or collection adjacent to the perforation site (41.9%, n=34). In patients where GB was already collapsed due to perforation with intra- abdominal collection, only PCD (18.5%, n=15) was placed. Those with distended GB and significant intra-abdominal collection underwent PCC & PCD (16.0%, n=13) or PCC with single-time aspiration due to a small collection (1.2%, n=1). If GB was not distended and no significant collection was noted, they were managed with intravenous antibiotics and other supportive care as indicated (22.22%, n=18). Cholecystectomy, either total or sub-total, was the most common surgical procedure performed (90.3%, 56/62). In 29 patients (46.7%, 29/62), laparoscopic surgery was done, out of which 5 patients (17.2%) underwent conversion to open, with the rest completed laparoscopically. When surgery was difficult to proceed laparoscopically, conversion to open surgery was also associated with difficulty, as observed in our case series where 80% (4/5) of converted patients underwent subtotal cholecystectomy. 6 patients due to suspicion of GBC malignancy in the pre-operative work-up underwent extended cholecystectomy (n=3) or anticipatory extended cholecystectomy (AEC) (n=3). AEC was performed on 3 patients with XGC on frozen section histology. Final histopathology showed adenocarcinoma in 2, XGC in 3 & granulomatous pathology in 1. AEC, popularly known as the 'Lucknow approach' in India, was published earlier by our centre where in open cholecystectomy with 2 cm liver wedge was resected en-bloc if thick-walled gallblad-

der was present on preoperative imaging to prevent a breach of tumour and was sent for frozen section analysis. If it turns out to be malignant, lymphadenectomy is also done. [17] 19 patients did not undergo surgery at our centre due to mortality at the time of initial presentation (n=3), operated elsewhere (n=7) and lost to follow-up (n=9). All GBC patients succumbed to metastatic disease during follow-up. Among operated patients, final histopathology revealed XGC in 32 (51.61%), CC in 23 (37.09%) and adenocarcinoma in 7 (11.29%). 7 operated patients (extended cholecystectomy - 2, laparoscopic subtotal cholecystectomy - 2, open subtotal cholecystectomy - 1, open cholecystectomy - 1, palliative cholecystectomy - 1) whose final histopathology did adenocarcinoma succumb to metastatic disease except one who died earlier due to complications of COVID-19 infection. Despite extensive pre-operative evaluation to rule out malignancy, some patients not suspected to have underlying malignancy due to post-perforation inflammatory changes already had malignancy on final histopathology. Despite undergoing surgery as per prevalent oncologic principles, GBC patients had a poor prognosis due to perforation causing the dissemination of malignant cells.

Conclusion

GBP is a rare presentation of various GB diseases, sometimes with underlying malignancy in disguise. Initial management requires aggressive control of sepsis and organ support. Evaluation for definitive surgery is crucial to decide the surgical plan. GBC perforation is associated with poor outcomes due to the dissemination of malignant cells and masquerading of malignancy due to post-GBP inflammatory changes. The proposed algorithmic approach can simplify treatment and help diagnose malignancy in these patients.

Ethics Committee Approval

It was a retrospective analysis of the prospective database, so no ethical clearance was sought.

Informed Consent

All patients came from India, and informed consent was taken.

Conflict of Interest

The authors have no conflicts of interest to declare.

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