

# Acute cholecystitis in neutropenic patients

Uriel Clemente-Gutiérrez, German Esteban Sánchez Morales, Paulina Moctezuma Velazquez, Alexandra Rueda de León Aguirre, Jesus Morales Maza, Ismael Dominguez-Rosado, and Heriberto Medina-Franco

Department of Surgery, National Institute of Health Sciences and Nutrition Salvador Zubirán, Mexico City, Mexico

**Backgrounds/Aims:** The frequency of acute cholecystitis reported in neutropenic patients is between 0.4-1.65%. Clinical manifestations differ from general population as well as clinical approach, diagnosis and treatment. The aim of this work is to describe clinical characteristics, diagnostic approach, and outcomes of patients with hematological diseases that presented with neutropenia and fever associated with acute cholecystitis in a tertiary referral hospital. **Methods:** We performed a retrospective analysis of patients with diagnosis of neutropenia and fever associated with acute cholecystitis in the period between January 2000 and January 2017. Quantitative variables were analyzed with mean and standard deviation, and qualitative variables with frequency and percentage. **Results:** During the study period, 2007 patients presented with neutropenia and fever. Twelve of them (0.59%) had associated acute cholecystitis. The most common hematologic disease among these patients was lymphoblastic leukemia. Acute acalculous cholecystitis was diagnosed in 6 cases (50%). Eleven patients (91.6%) had a severe presentation and cholecystostomy was performed in 9 (75%) cases. The main cause of mortality was septic shock (33.3%). **Conclusions:** Treatment of acute cholecystitis in patients with neutropenia must be individualized. Cholecystostomy should be considered as a bridge therapy for an interval cholecystectomy. (*Ann Hepatobiliary Pancreat Surg 2019;23:234-239*)

**Key Words:** Cholecystitis; Leukemia; Neutropenia

## INTRODUCTION

Abdominal infections in patients with neutropenia are usually severe and life-threatening.<sup>1</sup> Neutropenia may be due to a primary hematologic disorder or secondary to chemotherapy. The frequency of acute cholecystitis in this population is between 0.4-1.65% with a 30-day mortality of 26-48%,<sup>2</sup> being acalculous cholecystitis the most common presentation.<sup>3,4</sup>

Neutropenic enterocolitis is the most common intra abdominal infections associated with fever in neutropenic patients.<sup>5,6</sup> However, acute cholecystitis may have an atypical presentation in this patients and should always be considered as a differential diagnosis.<sup>7,8</sup>

Unfortunately there is scarce information on this topic on the literature and as a result there are no specific recommendations to guide diagnosis and treatment of acute

cholecystitis in hematologic diseases. The aim of this study was to describe the clinical characteristics, diagnostic approach, treatment, and outcomes of patients with hematological disorders, specifically neutropenia and fever associated with acute cholecystitis in a tertiary referral hospital.

## PATIENTS AND METHODS

A search was performed at our institution's electronic system to identify patients admitted to the hospital with the diagnosis of neutropenia and fever between January 2000 and January 2017. We included patients with diagnosis of acute cholecystitis. Neutropenia was defined according to the American Society of Hematology as an absolute neutrophil count below 1,500 cells/ $\mu$ l.<sup>9</sup> Diagnosis and severity of acute cholecystitis were established based

**Received:** July 10, 2018; **Revised:** November 10, 2018; **Accepted:** November 15, 2018

**Corresponding author:** Heriberto Medina-Franco

Department of Surgery, National Institute of Medical Sciences and Nutrition Salvador Zubirán, Vasco de Quiroga, 15 Col. Sección XVI. Del. Tlalpan C.P. 14000 México, D.F., México

Tel: +52-54870900, Fax: +52-55739321, E-mail: herimd@hotmail.com

Copyright © 2019 by The Korean Association of Hepato-Biliary-Pancreatic Surgery

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/4.0>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

Annals of Hepato-Biliary-Pancreatic Surgery • pISSN: 2508-5778 • eISSN: 2508-5859

on the Tokyo guidelines.<sup>10,11</sup> Quantitative variables were described with mean and standard deviation and qualitative variables with absolute frequencies and percentages.

## RESULTS

### General characteristics

Out of 2,007 patients hospitalized for neutropenia and fever 12 cases (0.59%) were associated with acute cholecystitis (Table 1). The median age was 35 years (21-70 years old), 5 patients were women (41.6%).

### Acute cholecystitis diagnosis and severity

All patients, except one who had no abdominal pain, met diagnostic criteria for acute cholecystitis according to Tokyo 2013 criteria. Acute acalculous cholecystitis was diagnosed in 6 individuals (50%). The most common local sign of inflammation was Murphy's sign in 7 patients (58.3%). Regarding systemic inflammatory response, fever and tachycardia were present in 9 patients (75%), and 5 patients (41.6%) had elevated C reactive protein. Abdominal ultrasound was performed in 10 patients (91.6%), and computed tomography in 2 (16.2%); findings were compatible with acute cholecystitis. Eleven patients (91.6%) presented with severe acute cholecystitis. Organ failures included hematological dysfunction (platelets  $< 100,000/\text{mm}^3$ ) in 11 patients (91.6%), cardiovascular dysfunction (hypotension requiring vasopressors) in 5 patients (41%), renal dysfunction (creatinine  $> 2.0$  mg/dl) in 4 patients (33.3%), and respiratory dysfunction (PaO<sub>2</sub>/FiO<sub>2</sub> ratio  $< 300$ ) in 2 patients (16.6%) Table 2.

### Hematologic characteristics

Concerning the hematologic diagnosis, seven patients (58.3%) had lymphoblastic leukemia, and acute myeloid leukemia, non-Hodgkin lymphoma, NK lymphoma, myelodysplastic syndrome (dendritic cell neoplasia), and aplastic anemia were present 1 patient (8.3%) each. Seven patients (58%) were under chemotherapy with Hyper-CVAD (hyperfractionated cyclophosphamide, vincristine sulfate, doxorubicin hydrochloride and dexamethasone), and the others with regimens that included cytarabine/rituximab, cyclosporine/bisulfan, or the SMILE scheme (dexamethasone, methotrexate, ifosfamide, L-asparaginase and etoposide). Regarding chemotherapy adverse effects,

grade 1-2 neurotoxicity was observed in two patients (16.6%) and grade 1-4 hematotoxicity in 11 (91.6%). Among those patients who received Hyper-CVAD therapy, grade 3-4 neutropenia and thrombocytopenia developed in all patients, and grade 1-2 anemia in five of them (71%).

The median time that elapsed between the last chemotherapy administration and the event of acute cholecystitis was 36.58 days (range 6-150). In preparation for cholecystostomy, 8 (88.8%), 1 (11.1%), and 1 (11.1%) patients were transfused with platelets, fresh frozen plasma, and red blood cells, respectively.

### Microbiology characteristics

*Escherichia coli* with extended-spectrum beta-lactamase (ESBL) was isolated from blood and bile cultures in 3 (25%), and 2 patients (16.6%), respectively. Other species isolated in bile included *Aeromonas hydrophila*, *Klebsiella pneumoniae* and *Staphylococcus aureus*.

### Treatment

Initially all patients received broad spectrum antibiotics, including carbapenems and vancomycin in most cases, as shown in Table 1. Cholecystostomy was performed in 9 patients (75%): the approach was percutaneous in 8 cases and open in one. Furthermore, 2 patients (16.6%) underwent laparoscopic cholecystectomy, and one (8.3%) received only medical treatment. It is worth to mention that 4 of the 5 patients with acalculous cholecystitis were treated with cholecystostomy tube and one of them was treated only with antibiotics. After four weeks three patients that were initially treated with cholecystostomy underwent interval laparoscopic cholecystectomy, and another patient had the cholecystostomy tube removed, with no complications. One patient still has a cholecystostomy in place.

### Outcomes

Four patients died (33.3%), three of them had undergone cholecystostomy and the patient that received only medical treatment died too. The cause of death was sepsis with multiorgan failure, one patient had concomitant neutropenic enterocolitis. Three out of 6 patients (50%) with acalculous cholecystitis died.

**Table 1.** Clinical characteristics in patients with hematologic malignancies and acute cholecystitis

Patient	Age/ gender	Diagnosis	Chemotherapy	Time interval last chemotherapy - acute cholecystitis diagnosis	Images study and diagnosis	Treatment	Antibiotics	Microbiological isolations
1	41/M	MDS	Danazol	22 days	US/acute calculos cholecystitis	Cholecystectomy	Ertapenem	Bile culture: <i>K. Pneumonie</i> , <i>S. saccharalyticus</i>
2	21/F	ALL Pre B	Hyper-CVAD	6 days	US/acute calculos cholecystitis	Cholecystectomy	Imipenem	None
3	18/M	ALL Pre B	Hyper-CVAD	12 days	US/acute acalculos cholecystitis	Percutaneous cholecystostomy	Piperacillin/tazobactam, vancomycin	Blood culture: <i>E.coli ESBL</i>
4	24/M	ALL Pre B	Hyper-CVAD	150 days	US/acute acalculos cholecystitis	Percutaneous cholecystostomy	Imipenem, vancomycin, fluconazole	Blood culture: <i>E.coli ESBL</i>
5	70/M	NHL	Cytarabine/rituximab	10 days	US/acute calculos cholecystitis	Percutaneous cholecystostomy	Meropenem, vancomycin	Bile culture: <i>E. coli ESBL</i> , <i>Aeromonas</i>
6	29/M	ALL Pre B	Hyper-CVAD	25 days	US/acute acalculos cholecystitis	Percutaneous cholecystostomy	Ertapenem	Blood culture: <i>E.coli ESBL</i>
7	38/F	ALL	Hyper-CVAD	11 days	CT/acute calculos cholecystitis	Open cholecystostomy	Piperacillin/tazobactam, vancomycin	Blood culture: <i>E.coli</i>
8	37/F	AML	-		US/acute acalculos cholecystitis	Medical treatment	Meropenem, vancomycin, amikacin, amphotericin	Blood culture <i>E.coli</i>
9	53/F	ALL Pre B	Hyper-CVAD	90 days	US/acute acalculos cholecystitis	Percutaneous cholecystostomy	Imipenem	None
10	34/M	Aplastic anemia	Cyclosporina/bisulfan	88 days	CT/acute calculos cholecystitis	Percutaneous cholecystostomy	Meropenem, vancomycin	None
11	23/F	ALL Pre B	Hyper-CVAD	14 days	US/acute acalculos cholecystitis	Cholecystectomy	Ceftazidime, amikacin, vancomycin	Blood culture: <i>S. aureus</i> , <i>Pseudomonas</i>
12	34/M	NK lymphoma	SMILE	11 days	US/acute calculos cholecystitis	Percutaneous cholecystostomy	Piperacillin/tazobactam, vancomycin	None

MDS, myelodysplastic syndrome; ALL, acute lymphoblastic leukemia; NHL, Non-Hodgkin lymphoma; AML, myeloid acute leukemia; US, Ultrasound scan; CT, Computed tomography; Hyper-CVAD, hyperfractionated therapy of cyclophosphamide, vincristine sulfate, doxorubicin hydrochloride (Adriamycin), and dexamethasone; SMILE, regimen of steroid (dexamethasone), methotrexate, ifosfamide, L-asparaginase, and etoposide

**Table 2.** Acute cholecystitis diagnosis and grading

Patient	Signs of local inflammation	Signs of systemic inflammation	Image study	Severity criteria
1	Positive, Murphy	Fever, tachycardia, elevated CRP 5.71	US, Gallbladder size: 10×5.6×5.7 cm, Wall thickness: 6 mm, Gallbladder stones presence, Pericholecystic fluid presence	Platelets < 100,000/mm <sup>3</sup>
2	Right upper quadrant pain	None	US, Gallbladder size: 11.4×4.8×4.2 cm, Wall thickness 2 mm, Gallbladder stone presence, Pericholecystic fluid absence	None
3	Positive, Murphy	Tachycardia	US, Gallbladder size: 12.1×4×4.2 cm, Wall thickness: 2.9 mm, Gallbladder stone absence, Pericholecystic fluid absence	Platelets < 100,000/mm <sup>3</sup> Creatinine > 2.0 mg/dl
4	Positive, Murphy	Fever, tachycardia	US, Gallbladder size: 10.3×4.8×4.3 cm, Wall thickness: 8 mm, Gallbladder stone absence, Pericholecystic fluid presence	Platelets < 100,000/mm <sup>3</sup> Hypotension requiring vasopressors
5	Right upper quadrant pain	Fever, tachycardia, elevated CRP 9.13	US, Gallbladder size: 11.2×4.3×3.1 cm, Wall thickness: 5.2 mm, Gallbladder stone presence, Pericholecystic fluid presence	Platelets < 100,000/mm <sup>3</sup> Hypotension requiring vasopressors Creatinine > 2.0 mg/dl
6	Positive, Murphy	Fever, tachycardia, elevated CRP 28.4	US, Gallbladder size: 13×6.2×4.2 cm, Wall thickness: 3.2 mm, Gallbladder stone absence, Pericholecystic fluid absence	Platelets < 100,000/mm <sup>3</sup> Hypotension requiring vasopressors PaO <sub>2</sub> /FiO <sub>2</sub> ratio < 300
7	None	Fever, tachycardia	CT, Gallbladder size: 7.3×4.5×2.7 cm, Wall thickness: 10 mm, Gallbladder stone presence, Pericholecystic fluid presence	Platelets < 100,000/mm <sup>3</sup> Hypotension requiring vasopressors Creatinine > 2.0 mg/dl PaO <sub>2</sub> /FiO <sub>2</sub> ratio < 300
8	Right upper quadrant pain	Fever, tachycardia	US, Gallbladder size: 3.13×8.26×3.3 cm, Wall thickness: 4.3 mm, Gallbladder stone absence, Pericholecystic fluid presence	Platelets < 100,000/mm <sup>3</sup> Hypotension requiring vasopressors Creatinine > 2.0 mg/dl PaO <sub>2</sub> /FiO <sub>2</sub> ratio < 300
9	Positive, Murphy	Elevated CRP 14	US, Gallbladder size: 11.6×4.3×4.6 cm, Wall thickness: 2 mm, Gallbladder stone absence, Pericholecystic fluid absence	Platelets < 100,000/mm <sup>3</sup>
10	Positive, Murphy	Fever, tachycardia	US, Gallbladder size: 8.3×3.5×4 cm, Wall thickness: 3.3 mm, Gallbladder stone presence, Pericholecystic fluid presence	Platelets < 100,000/mm <sup>3</sup>
11	Positive, Murphy	Fever, tachycardia	CT, Gallbladder size: 4.4×3.2×2.7 cm, Wall thickness: 3 mm, Gallbladder stone absence, Pericholecystic fluid presence	Platelets < 100,000/mm <sup>3</sup>
12	Right upper quadrant pain	Fever, tachycardia, elevated CRP 16.3	US, Gallbladder size: 7.4×3.2×2.8 cm, Wall thickness: 6 mm, Gallbladder stone presence, Pericholecystic fluid presence	Platelets < 100,000/mm <sup>3</sup>

US, Ultrasound; CT, Computed tomography; CRP, C reactive protein

## DISCUSSION

Abdominal pain in patients with neutropenia might require an exhaustive approach due to its broad differential diagnosis and atypical presentation among these patients,<sup>12</sup> who may not present an inflammatory response. Despite neutropenic enterocolitis being the most common etiology in this scenario,<sup>13</sup> acute cholecystitis should be considered as a differential diagnosis.<sup>14</sup> It is thought that the smaller mucosal surface of the gallbladder compared with the colon might explain the low frequency of acute cholecystitis

as etiology of abdominal pain in neutropenic patients with fever.<sup>1</sup> Our study showed a frequency of 0.59% without male or female predominance, similar to the reported in other series.<sup>15</sup> Acalculous cholecystitis was documented in 50% of the cases, compared to 55-65% in other series.<sup>16</sup> In non-neutropenic patients acalculous cholecystitis is much less frequent, comprising roughly 5% of the cases of acute cholecystitis. This may be because patients with neutropenia have several risk factors for this presentation such as bile stasis, prolonged fasting, and increased intraluminal pressure.<sup>2,8</sup>

**Table 3.** Treatment, complications and transfusion requirements

Patient	Treatment	Complications	Clavien Dindo.	Transfusion requirement	Interval cholecystectomy	Mortality
1	Cholecystectomy	Acute cholangitis	I Ib	Platelets transfusion×2	-	No
2	Cholecystectomy	None	-	None	-	No
3	Cholecystostomy	Septic shock	V	Platelets transfusion×1 Red blood cells transfusion×2	No	No
4	Cholecystostomy	None	-	Platelets transfusion×1 Red blood cells transfusion×1	No	Neutropenic enterocolitis
5	Cholecystostomy	None	-	Red blood cells transfusion×1	No	No
6	Cholecystostomy	None	-	Platelets transfusion×2 Red blood cells transfusion×1	Laparoscopic cholecystectomy	No
7	Cholecystostomy	Hepatic subcapsular hematoma	I	Platelets transfusion×1 Red blood cells transfusion×1	Open cholecystectomy	No
8	Antibiotics	Multiorgan failure	V	Fresh frozen plasma transfusion×4	-	Septic shock
9	Cholecystostomy	None	-	None	Laparoscopic cholecystectomy	Septic shock
10	Cholecystostomy	Multiorgan failure	V	Platelets transfusion×1	No	Septic shock
11	Cholecystectomy	None	-	Platelets transfusion×1 Red blood cells transfusion×2	-	No
12	cholecystostomy	None	-	Platelets transfusion×1	Laparoscopic cholecystectomy	No

Treatment decision between surgical cholecystectomy or percutaneous cholecystostomy in these patients is troublesome since most of them fulfill criteria for severe acute cholecystitis and might require the former according to Tokyo recommendations,<sup>11</sup> however, there is not enough evidence to recommend one procedure over the other in this specific population. All our patients met Tokyo criteria for acute cholecystitis, and 11 patients (91%) were classified as severe based on hematological failure resulting either from their underlying disease or from chemotherapy induced myelosuppression, but probably not because of severe sepsis, which questions the validity of these criteria in this specific population. As a matter of fact, hematologic failure was the only criteria of severity in 5 of 11 patients. Hematologic disease is an important factor to consider when planning treatment because most patients will need transfusion of blood products prior to any invasive procedure. In our study ten patients (83.3%) required blood products including platelets transfusion in 8 patients (88.8%), fresh frozen plasma in 1 patient (11.1%) and red blood cells transfusion in 1 patients (11.1%).

Concerning treatment (Table 3), cholecystostomy was performed in 9 patients (75%), laparoscopic cholecystectomy in 2 (16.6%), and one patient received only medical treatment. Mortality in our series was 33.3%,

which is in line with the 26-48% reported in previous studies.<sup>17</sup> Septic shock was the main cause of death. There were no deaths in the laparoscopic cholecystectomy group, while three patients in the cholecystostomy group (37%), and one in the antibiotic treatment group died. According to these results, surgical cholecystectomy or percutaneous cholecystostomy may be more beneficial than antibiotic treatment alone. Mortality was higher in acalculous presentation when compared to calculous cholecystitis (50% versus 16.6%, respectively) probably explained by the fact that the former represents a group of patients with a more severe disease or with a delayed diagnosis.

In conclusion, acute cholecystitis in neutropenic patients is a rare diagnosis, accounting for less than 1% of the neutropenic fever admissions. Among this group of patients, acalculous cholecystitis is more frequent than in general population. Blood and bile cultures should be obtained so it can help to guide antimicrobial therapy. Since there are no guidelines for acute cholecystitis in neutropenic patients, their treatment should be individualized, for those with acalculous cholecystitis cholecystostomy tube placement is preferred; those presenting with calculous cholecystitis can be treated either with cholecystostomy tube if the patient is unstable or laparoscopic cholecystectomy if the patient's general condition allows it.

## REFERENCES

1. Gorschlüter M, Mey U, Strehl J, Schepke M, Lamberti C, Sauerbruch T, et al. Cholecystitis in neutropenic patients: retrospective study and systematic review. *Leuk Res* 2006;30:521-528.
2. Büyükaşık Y, Koşar A, Demiroğlu H, Altınok G, Özcebe OI, Dündar S. Acalculous acute cholecystitis in leukemia. *J Clin Gastroenterol* 1998;27:146-148.
3. Orlando R 3rd, Gleason E, Drezner AD. Acute acalculous cholecystitis in the critically ill patient. *Am J Surg* 1983;145:472-476.
4. Howard RJ. Acute acalculous cholecystitis. *Am J Surg* 1981;141:194-198.
5. Gorschlüter M, Mey U, Strehl J, Schmitz V, Rabe C, Pauls K, et al. Invasive fungal infections in neutropenic enterocolitis: a systematic analysis of pathogens, incidence, treatment and mortality in adult patients. *BMC Infect Dis* 2006;6:35.
6. Picardi M, Selleri C, Camera A, Catalano L, Rotoli B. Early detection by ultrasound scan of severe post-chemotherapy gut complications in patients with acute leukemia. *Haematologica* 1999;84:222-225.
7. Starnes HF Jr, Moore FD Jr, Mentzer S, Osteen RT, Steele GD Jr, Wilson RE. Abdominal pain in neutropenic cancer patients. *Cancer* 1986;57:616-621.
8. Vaughn EA, Key CR, Sterling WA Jr. Intraabdominal operations in patients with leukemia. *Am J Surg* 1988;156:51-53.
9. Valent P. Low blood counts: immune mediated, idiopathic, or myelodysplasia. *Hematology Am Soc Hematol Educ Program* 2012;2012:485-491.
10. Miura F, Takada T, Kawarada Y, Nimura Y, Wada K, Hirota M, et al. Flowcharts for the diagnosis and treatment of acute cholangitis and cholecystitis: Tokyo guidelines. *J Hepatobiliary Pancreat Surg* 2007;14:27-34.
11. Miura F, Takada T, Strasberg SM, Solomkin JS, Pitt HA, Gouma DJ, et al. TG13 flowchart for the management of acute cholangitis and cholecystitis. *J Hepatobiliary Pancreat Sci* 2013;20:47-54.
12. Trowbridge RL, Rutkowski NK, Shojania KG. Does this patient have acute cholecystitis? *JAMA* 2003;289:80-86.
13. Wade DS, Nava HR, Douglass HO Jr. Neutropenic enterocolitis. Clinical diagnosis and treatment. *Cancer* 1992;69:17-23.
14. Kuttah L, Weber F, Creger RJ, Fox RM, Cooper BW, Jacobs G, et al. Acute cholecystitis after autologous bone marrow transplantation for acute myeloid leukemia. *Ann Oncol* 1995;6:302-304.
15. Wasserheit C, Acaba L, Gulati S. Abnormal liver function in patients undergoing autologous bone marrow transplantation for hematological malignancies. *Cancer Invest* 1995;13:347-354.
16. Teefey SA, Kimmey MB, Bigler SA, Trowers EA, Sillery JK. Gallbladder wall thickening: an in vitro sonographic study with histologic correlation. *Acad Radiol* 1994;1:121-127.
17. Storti S, Marra R, Pagano L, Sica S, Borzone, Cagossi M, et al. Emergency abdominal surgery in patients with acute leukemia and lymphoma. *Ital J Surg Sci* 1988;18:361-363.