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Acute acalculous cholecystitis complicating chemotherapy for acute myeloblastic leukemia

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ABSTRACT

Acute acalculous cholecystitis is a rare complication in the treatment of acute myeloblastic leukemia. Diagnosis of acute acalculous cholecystitis remains difficult during neutropenic period. We present two acute myeloblastic leukemia patients that developed acute acalculous cholecystitis during chemotherapy-induced neutropenia. They suffered from fever, vomiting and acute pain in the epigastrium. Ultrasound demonstrated an acalculous gallbladder. Surgical management was required in one patient and conservative treatment was attempted in the other patient. None treatment measures were effective and two patients died. Acute acalculous cholecystitis is a serious complication in neutropenic patients. Earlier diagnosis could have expedited the management of these patients.

1. Introduction

Acute acalculous cholecystitis (ACC) is defined as an acute necroinflammatory disease of the gallbladder in the absence of cholelithiasis and has a multifactorial pathogenesis [1]. ACC has very rarely been described in patients undergoing myelosuppressive chemotherapy for acute myeloblastic leukemia (AML). As far as the latter patients are concerned, expecting severe neutropenia lasting for ≥ 10 days, ACC is associated with significant morbidity and mortality [2]. Clinical diagnosis of ACC remains difficult in these patients' populations, but early diagnosis and intervention can boost prognosis. We present two AML patients that developed ACC during chemotherapy-induced neutropenia.

Case report 1: A 21-year-old male was admitted to our hospital for AML. The patient started chemotherapy with cytarabine 200 mg/m^2 in a 24 h infusion through days 1 to 7 and idarubicin 12 mg/m^2 (days 1,2,3). In neutropenic period, he developed invasive pulmonary aspergillosis treated with voriconazole and *Stenotrophomonas maltophilia* bacteremia that resolved with broad spectrum antibiotics. The bone marrow examination on the 25th days of induction showed persisting infiltration with 50% blasts. The patient, then, underwent a second course of induction chemotherapy with high dose of cytarabine 6 g/m^2 (days 1,2,3) and Metoxantrone 12 mg/m^2 (days 1,2,3). He received voriconazole during chemotherapy for secondary prophylaxis of probable invasive aspergillosis. On day 9 of the second course, he presented febrile neutropenia that has been aggravated by septic shock. Broad spectrum antibiotic regimen and intravenous crystalloid fluid were administered. The values of peripheral blood pressure responded well to fluids. *Enterobacter cloacae* were detected in peripheral blood. However, the patient was still febrile. On day 20, he was diagnosed with acute pain in the right upper quadrant accompanied by vomiting. His leukocyte count was 0.5×10^9/L and absolute neutrophil count was 0.0×10^9/L. C-reactive protein was 260 mg/dL. His renal function was normal, and liver function tests result showed cholestasis without cytolysis. Abdominal ultrasonography was performed and demonstrated acalculous gallbladder with overdistention, wall thickening (up to 5 mm). ACC was diagnosed and the medical therapy continued (broad spectrum antibiotic regimen, intravenous fluids, fasting). Nevertheless, the patient's condition deteriorated and on the next day, he presented abdominal contracture. A second abdominal ultrasound demonstrated acalculous gallbladder with overdistention, wall thickening (up to 11 mm) and pericholecystic fluid (Fig. 1). The patient was qualified for life-saving surgery. Open-cholecystectomy was performed after platelet concentrate transfusions. The intraoperative examination revealed a gangrenous acalculous cholecystitis that had reached the cystic duct and an under hepatic blade. Histopathological evidence demonstrated gangrenous cholecystitis. In the postoperative period, a broad spectrum antibiotic

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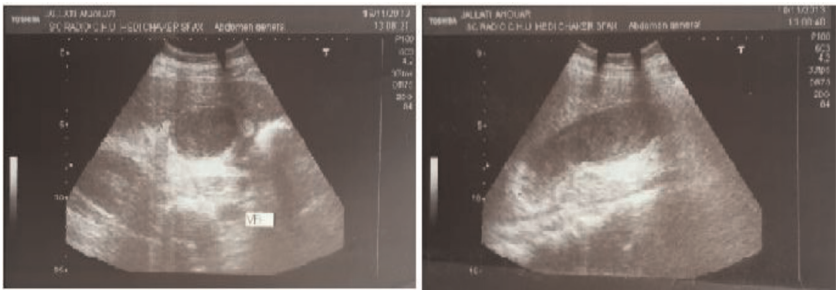

Fig. 1. Ultrasound appearance of thickened wall gallbladder.

regimen, erythrocyte and platelet concentrate transfusions were continued. However, the patient was still febrile. Chest X-ray demonstrated an intensive bilateral pneumonia. Then, the patient presented a respiratory distress syndrome and he died on post-operative day 5.

Case report 2: A 52 year old female was followed up at our hospital for AML. She was in remission after induction chemotherapy. The course was complicated by invasive pulmonary aspergillosis treated with Voriconazole. Then, she received a first course of consolidation. During neutropenic period, she presented a bacteremia to *Burkhaldaria cepacia*. The patient was treated with broad spectrum antibiotic. A second course of consolidation was administrated with cytarabine 200 mg/m^2 in a 24 h infusion through days 1–7; daunorubicin 50 mg/m^2 (days 1,2,3) and etoposide 100 mg/m^2 in a 4-h infusion every 24 h from day 1 to day 5. She received voriconazole during chemotherapy for secondary prophylaxis of probable invasive aspergillosis. Nine days after chemotherapy, the patient presented a febrile neutropenia with worsening diarrhea, intermittent nausea, vomiting, and acute abdominal pain. She received a combination of antibiotic therapy and imipenem, amikacin. Blood cultures were negative. She remained febrile. On the 21 day after the start of chemotherapy, while the patient was under broad-spectrum antibiotic treatment, the symptoms recurred; fever accompanied by vomiting and acute pain in the right upper quadrant. Laboratory examination revealed the following results: C-reactive protein increased to 450 mg/l, absolute neutrophil count was 0.0×10^9/L and platelets count 0.8×10^9/L, accompanied by elevated blood levels of cholestatic liver enzymes without cytolysis with a total bilirubin of 163 micromol [4–24 μmol]. Abdominal ultrasonography and computer tomography confirmed the diagnosis of ACC by showing gallbladder with overdistention, wall thickening (mm) and biliary sludge (Fig. 2). ACC was diagnosed, and the medical therapy was continued (broad spectrum antibiotic regimen, intravenous fluid, fasting). However, the patient's condition deteriorated and she died by septic shock after 5 days of ACC diagnostic.

2. Comments

The present two cases developed ACC during chemotherapy induced neutropenic for AML. ACC is a relatively rare complication in these patients' population. It's reported in 0.4% among all neutropenic episodes of patients with acute leukemia or aggressive lymphoma undergoing myelosuppressive chemotherapy [3]. Clinically, AAC is difficult to diagnose because the findings of right upper-quadrant pain, fever, leukocytosis, and abnormal liver tests are not specific. Diagnosis of ACC may be further prolonged until the patient's general condition worsens as a consequence of gallbladder necrosis or perforation, as our two cases. Ultrasound is an established valuable imaging method if cholecystitis is suspected [4]. Computed tomography can be extremely useful in the assessment of septic shock of unknown origin in this patient population [4]. In the present two cases, we observed several factors that were most likely responsible for ACC. These included chemotherapy, neutropenia, fasting, fever, diarrhea and bacteremia. The latter factors induced intracystic hemorrhage followed by sudden exacerbation, which resulted in gangrenous cholecystitis followed by perforative biliary peritonitis [2]. Similar finding was observed in our first case report. Voriconazole recommended for treatment of invasive aspergillosis, were associated with significant increasing toxic adverse effect. Cholecystitis was reported in few patients exposed to voriconazole medication [5]. Our two patients were treated with voriconazole during the course of chemotherapy. Voriconazole might have increased the risk of cholecystitis in our two patients. The two prevailing treatment options for AAC are cholecystostomy and/or cholecystectomy [2]. However, there was a hot debate as to its optimal effectiveness in the treatment of ACC. Consequently, Cholecystostomy does not offer a survival benefit compared with cholecystectomy or no surgical interventions in patients with ACC [6]. Several studies have found improved outcomes in patients with cholecystectomy compared with patients without surgical management [6]. Early cholecystectomy eliminated the potential infection foci, and

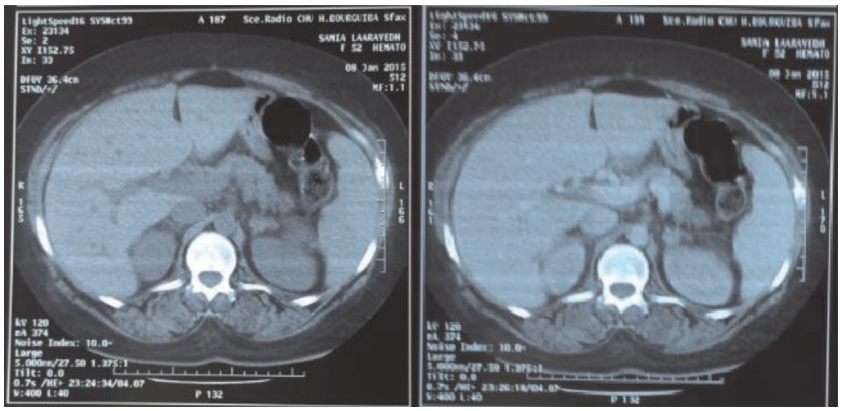

Fig. 2. Computed axial tomography demonstrating thickening of the gallbladder with surrounding edema and inflammation.

reduced the risk of ongoing sepsis and multi-organ failure [2]. In our first case, the ultrasound image was suggestive of gall bladder necrosis, with biliary perforation and this was confirmed in intraoperative. In the second case, the operation wasn't performed urgently, and the patient died by septic shock. These two presented cases confirm that ACC can progress into a very serious condition with high risk of mortality if gangrene and perforation developed.

3. Conclusion

There are several risk factors for gallbladder-related surgical emergencies in patients with acute leukemia. Although ACC is rare, it should be added to be the list of main causes leading to acute abdominal pain in neutropenic patients and unexplained fever. These two cases at hand, also demonstrate that ACC is associated with poor short term outcome in neutropenic patients. Early diagnosis and treatment may lead to better outcomes.

Conflict of interest

None.

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