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ACALCULOUS CHOLECYSTITIS IN A PATIENT WITH PLASMODIUM FALCIPARUM MALARIA AND CYTOMEGALOVIRUS INFECTION

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Abstract

Acalculous cholecystitis is a syndrome of gallbladder inflammation without gallstones, recognized within the setting of critically ill patients. Acalculous cholecystitis associated with infectious agents is reported in the literature to be rare. Herein we describe a case of acalculous cholecystitis in a patient with malaria caused by *Plasmodium falciparum* and apparent cytomegalovirus infection, and discuss the possible role of CMV in the pathogenesis of acalculous cholecystitis in patients with malaria.

Keywords: acalculous cholecystitis, malaria, plasmodium falciparum, cytomegalovirus

Introduction

Acalculous cholecystitis (AC) is a syndrome of gallbladder inflammation without gallstones.

The syndrome is most commonly recognized within the setting of critically ill patients, especially related to trauma, surgery, shock, burns, sepsis, total parenteral nutrition, and/or prolonged fasting [1]. AC owing to infectious agents is reported in the literature to be rare [2-7]. AC has been observed in malaria [8].

More recent studies have suggested that AC may occur without an identifiable precipitant [9]. Clinically, AC is difficult to diagnose because clinical findings (right upper-quadrant pain, fever, leukocytosis and abnormal liver tests) are variable and nonspecific. The pathogenesis of AC is complex and multifactorial. Diagnostic imaging of the gallbladder is essential in establishing the diagnosis of AC. Either sonography or computed tomography that demonstrates pericholecystic fluid or > 3,5 mm thickening of the gallbladder wall in the absence of hypoalbuminemia or ascites is strongly suggestive of AC [10]. The recommended treatment of AC is immediate hemodynamic stabilization and initiation of broad spectrum antibiotics followed by prompt percutaneous cholecystostomy [11].

We describe a case of AC in a patient with malaria caused by *Plasmodium falciparum*, who tested positive for CMV infection. We discuss the possible role of CMV in the pathogenesis of AC in patients with malaria.

Case

A 52-year-old Ghanaian woman presented to the emergency department because of abdominal pain and fever. The patient's acute illness started 5 days before admission, with fever of 39°C, chills and abdominal pain without vomiting or nausea. Her symptoms began ~15 days after returning from an 11-month trip to Ghana.

On admission she was ill but without an altered state of consciousness with a temperature of 39°C, heart rate of 98 bpm, respiratory rate 28 breaths per minute, and blood pressure of 120/60 mmHg. Physical examination findings were significant for pain in the gallbladder and epigastric region. She had no hepato-splenomegaly. There were no signs of meningeal irritation, cognitive impairment or any neurological deficit.

Laboratory studies showed a white blood cell (WBC) count of 24.200/mm^3 (neutrophils 89.7%, lymphocytes 5.5%); hemoglobin level 8.6 g/L; platelets count 17.000/mm^3; C-Reactive protein 198 mg/L; total bilirubin 9,73 mg/dL; direct bilirubin 8,66 mg/dL; aspartate aminotransferase (AST) 126 IU/L; alanine aminotransferase (ALT) 58 IU/L; alkaline phosphatase (ALP) 325 IU/L; Gamma-glutamyl transpeptidase (ɣ-GT) 205 IU/L; serum amylase and lipase 143 IU/L and 93 IU/L respectively; D-dimer 15.112 ng/mL. Examination of a blood thin smear was negative for spirochaete but revealed ring trophozoites typical of *P. falciparum* including multiple infected cells with 3.7% of erythrocytes parasitized. Also the antigen test resulted positive for *P. falciparum*.

Abdominal ultrasound showed a thickened gallbladder wall (3.5 mm) surrounded by a thin rim of fluid. No stones were visible and a diagnosis of acalculous cholecystitis was made. Mild splenomegaly was also noted on ultrasound. Abdominal computed tomography (CT) confirmed the diagnosis, showing an 8 mm diameter common bile duct and a mild biliary ductal dilatation (Figure 1). Chest CT showed a moderate pleural effusion on the right and a minimum pleural effusion on the left, associated with areas of parenchymal consolidation in the right apical segment and the apical segment of the ipsilateral lower lobe. QuantiFERON-TB-Gold test and viral serology for HIV were negative.

The patient was treated immediately with a co-formulation of dihydroartemisinin-piperaquine 120 mg/960 mg qd po for three days. Intravenous meropenem 1 gr tid ev and doxycicline 100 mg bid po were also started before the peripheral smear was obtained because of concern that there might be intra-abdominal and pneumonial infection. Microscopy after Ziehl-Neelsen (ZN) staining of three sputum samples yielded a negative result for mycobacteria.

Four days after initiation of anti-malaria therapy, the patient's clinical condition improved,

even if mild fever and abdominal discomfort persisted for a week; AST and ALT, though still mildly elevated, had decreased, together with total bilirubin levels, ALP and ɣ-GT. Blood smear examination was repeated at the end of anti-malaria therapy and the result was negative for malarial parasites. Laboratory analysis showed the presence of IgM and IgG for cytomegalovirus. Antibiotic therapy was stopped after two weeks. Repeat abdominal CT prior to discharge did not reveal any gallbladder pathology. The patient was discharged on the fourteenth day in good health.

Discussion

Over the last two decades, immigration has been a growing phenomenon in Italy, and in Sicily in particular due to its proximity to the African continent. Migration could increase the risk of malaria transmission and lead to it being reintroduced in areas where it had previously been eradicated [12,13,29].

AC occurring during malaria infection has rarely been reported [8]. The rarity of AC in malaria patients may be due to under-reporting, since the symptoms and signs of AC (abdominal pain, fever, vomiting, jaundice and leukocytosis) are non-specific and mimic the symptoms associated with *Plasmodium* parasite infection; routine abdominal ultrasonography is not done and many cases of AC are probably missed.

The pathophysiology of AC in association with malaria is multifactorial. Patients with malaria are predisposed to increased bile viscosity due to fever and dehydration and because of the absence of oral feeding (due to anorexia, vomiting, mental confusion or even coma), leading to decreased gallbladder contraction and consequent bile stasis. Furthermore, the phenomenon of aggregation of parasitized red blood cells to non-parasitized cells (rosetting) and adherence of parasitized red blood cells to vessel walls might explain the pathogenesis of AC in malaria by *P. falciparum* and *P. vivax* [14-18]. Indeed, *Plasmodium vivax* exhibits a cytoadherence phenomenon in which infected erythrocytes bind endothelial receptors in a similar fashion to *P. falciparum* [19]. Malaria, like other arthopod-borne diseases and some anthropozoones, can cause HLH [30-34].

Another mechanism that may play a role in and account for malaria-related AC in both infections is the imbalance of pro-inflammatory and anti-inflammatory cytokines that occurs during malaria [20-22]. There are few studies on *P. malariae* pathogenesis [19]. Louse-Borne Relapsing Fever (LBRF) by Borrelia recurrentis should be considered among clinical hypotheses in migrants with similar clinical presentation [23].

We describe a case of AC in a patient with *P. falciparum* malaria and CMV infection.

In this instance, antimalarial therapy worked; no parasites were detected microscopically following treatment. However, the patient continued to have mild fever and abdominal tenderness for another week. IgM and IgG positivity for CMV raised the suspicion that immunologically-diagnosed CMV infection could have played a role in the protracted course of symptoms and in AC in a patient carrying the haplotype or the HLABw4(T) allele at higher risk of developing CMV symptomatic disease [24,25,35-38].

P. falciparum malaria profoundly affects the host's immune system by mediating at the same time immuno-suppression and immune hyper-activation, that can cause reactivation and shedding of all known human herpes viruses. While an association between malaria and Epstein-Barr Virus (EBV) reactivation has already been established, any association between malaria and CMV has yet to be demonstrated [26,27]. In our patient, IgM and IgG positivity for CMV could mean an acute infection or a transient viral reactivation due to immunosuppression induced by malaria. Therefore, CMV may have played a significant role in the pathogenesis of the AC. However, to the best of our knowledge, CMV has been documented as cause of AC in children and immunodepressed patients [27,28], but has never been associated with AC in immunocompetent adult patients.

In conclusion, AC in our patient was probably malaria-associated. Whether acute CMV infection or latent viral activation also contributed to AC in this case is not known.

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