Acalculous Cholecystitis in a Patient With *Plasmodium falciparum* Infection: A Case Report and Literature Review

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Acute acalculous cholecystitis (AAC) can occur without gallstones in critically ill or injured patients and has also been associated with various infectious agents.[1–4] We report here a case of AAC in a patient with *Plasmodium falciparum* malaria.

Case Report

A 24-year-old Cameroonian female was admitted with a 4-day history of fever, headache, nausea, vomiting, and diffuse abdominal pain. The symptoms appeared 3 weeks after she had returned from Cameroon. It was her first trip back home in 9 years. On admission, her temperature was 39.5°C, her pulse 118 beats/min, and her blood pressure 95/50 mm Hg. Physical examination revealed tenderness on abdominal palpation.

Laboratory studies showed white blood cell (WBC) count of 4.1 × 10^9/L, hemoglobin level of 107 g/L, and platelet count of 38 × 10^9/L. The C-reactive protein (CRP) was 18 mg/dL (Normal value [N1] < 1 mg/dL). Serum aspartate aminotransferase (AST) level was 43 IU/L (Nl < 33 IU/L). Examination of blood thin smear revealed infestation with ring trophozoites, typical of *Plasmodium falciparum* with 6% of erythrocytes being parasitized. Treatment with intravenous quinine and oral doxycycline was started. Because of vomiting, doxycycline was replaced by intravenous clindamycine. Two days after, the percentage of erythrocytes parasitized was 1%, but the patient was still febrile (39.5°C). Physical examination showed increased pain and inspiratory arrest on subcostal palpation of the right upper quadrant. Liver function tests showed mildly elevated AST at 50 IU/L (Nl < 33 IU/L), alanine aminotransferase (ALT) at 70 IU/L (Nl < 63 IU/L) in the presence of a total bilirubin level of 1.5 mg/dL (Nl < 1.2 mg/dL), and a direct bilirubin level of 0.5 mg/dL (Nl < 0.2 mg/dL). The WBC count was normal (4.2 × 10^9/L) in the presence of a CRP level of 21 mg/dL. An abdominal ultrasonography revealed a thickened gallbladder wall (10 mm) in the absence of calculi and in the presence of ultrasonographic Murphy sign, defined as maximum tenderness over the sonographically localized gallbaldder. Intravenous cefuroxime and metronidazole were started. Within 24 hours, the fever as well as the abdominal pain disappeared. The treatment was completed with atovaquone/proguanil, and the patient was discharged after 3 days.

Discussion

This is the fourth, well-documented case of malaria-related acute acalculous cholecystitis (AAC).[4–5] They were one Caucasian and two African females living in nonendemic area for many years before traveling to Africa. They were 46, 24, and 26 years of age, respectively. One case has also recently been described in a 7-year-old girl living in India.[6] They had

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history of nausea, vomiting, abdominal pain, and sometimes diarrhea. The blood smear revealed heavy infestation (from 6% to 30% of red blood cells) by *P falciparum* and coinfection by *P vivax* in one case. Other laboratory analysis revealed a WBC count ranging from 4.1×10^9/L to 10.1×10^9/L in the presence of normal or mildly elevated hepatic enzymes. Abdominal ultrasonography revealed a thickened gallbladder wall (5–10 mm) together with sludge, high density bile, or pericholecystic fluid collection (one case). Medical treatment of malaria and/or antibiotherapy result in resolution of AAC without need for cholecystectomy or cholecystostomy.[4–6]

A fifth case has also been described in a 24-year-old woman.[7] However, when the diagnosis of AAC was made, three blood smears for parasites were negative in the absence of hemolysis signs. Furthermore, clinical improvement and ultrasound findings normalization were observed after antibiotic administration in the absence of any malaria treatment.

In the absence of malaria, AAC represents 2% to 15% of cholecystectomies performed for acute cholecystitis. AAC occurs mostly in critically ill or injured patients. Risk factors include trauma, burns, sepsis, shock, diabetes, abdominal vasculitis, and hyperalimentation. The presentation of AAC may be insidious. Ultrasonography is the most accurate diagnostic modality, computerized tomography being reserved for patients with negative ultrasonography. Given the frequency of complications (gangrene, abscess, cholangitis, or perforation) and the high mortality rate (between 10 and 50%), treatment consists of cholecystectomy, ultrasound-guided percutaneous cholecystostomy, or, exceptionally, endoscopic therapy with nasobiliary drainage. Patients receive concomitantly antibiotherapy based on the results of bile cultures. The pathogenesis of AAC is complex, but ischemia and reperfusion injury, the effects of eicosanoid proinflammatory mediators appear to be the central mechanisms.[3,8–9] Bile stasis (resulting in increased concentration of the detergent bile salts leading to histotoxicity to the gallbladder mucosa) has also been implicated.[10]

Once it occurs, infection usually represents a secondary event and involves Gram-negative enteric flora. However, in some patients, infection may be the primary event as it has been described with *Salmonella* sp, *Staphylococcus aureus*, *Mycobacterium tuberculosis*, *Brucella* sp, *Candida* sp, Cytomegalovirus, Dengue virus, *Vibrio cholerae*, *Leptospira* sp, *Shistosoma* sp, *Rickettsia* sp, *Coxiella* sp, *Isospora* sp, *Cyclospora* sp, *Cryptosporidium* sp, *Microsporidium* sp, and *Leishmania* sp.[3,11–22]

In the context of malaria, the three pathophysiologic mechanisms are present.

First, Sequestration of parasites in the gallbladder microvasculature,[23] reduction of hepatic blood flow, anemia, and fluid losses may be involved in gallbladder ischemia.

Second, the fasting state is known to predispose to biliary stasis.

Finally, sequestration of infected erythrocytes is thought to initiate the local production of inflammatory cytokines and mediators.[24]

Conclusion

In conclusion, AAC is a rare complication of *P falciparum* malaria. Clinical and biological findings are poorly specific, and the diagnosis of AAC remains a challenge. Ultrasound of the gallbaldder should be considered in patient with right upper quadrant tenderness, persistent fever, leukocytosis, hyperamylasemia, or abnormal aminotransferases.

Although cholecystectomy or cholecystostomy remain the mainstay of therapy, the review of four cases suggests that in young patients without underlying disease, AAC could be successfully treated, under close monitoring, by antimalarial and antibiotic treatment without surgical intervention. However, in the absence of larger cases studies and because of the high rate of complications observed in non–malaria-related AAC, surgery should always be considered especially in critically ill patients, particularly older patients with a high WBC count,[25] in patients with complicated AAC, in patients not responding rapidly to medical treatment, and in the presence of conditions predisposing to gallbladder ischemia.

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Declaration of interests

The authors state that they have no conflicts of interest.

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