Am. J. Trop. Med. Hyg., 85(1), 2011, pp. 42–49
doi:10.4269/ajtmh.2011.10-0724

Case Report: Malaria Caused by *Plasmodium vivax* Complicated by Acalculous Cholecystitis

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Abstract. We report the first adult cases of acute acalculous cholecystitis (AAC) exclusively caused by infections with *Plasmodium vivax*. We reviewed the previous cases of AAC occurring during malaria, compared and contrasted the variables of previously reported cases with the cases reported here, examined the pathogenic link between malaria and AAC, and considered the diagnostic pitfalls and treatment implications as they applied to clinical outcomes in patients with this serious and potentially underrecognized illness.

INTRODUCTION

We report two cases of acute acalculous cholecystitis (AAC) in adults occurring during malaria caused by *Plasmodium vivax*. Acute acalculous cholecystitis occurring during malaria has been reported rarely. Previously reported cases have included 11 cases of AAC occurring during *Plasmodium falciparum* infections, two cases of AAC in an adult reported to be co-infected with *P. falciparum* and *P. vivax*, and a case of AAC in a child with malaria caused by *P. vivax*. The cases reported here are the first adult cases of AAC attributed solely to infections with *Plasmodium vivax*.

CASE REPORT 1

A 26-year-old male, Caucasian, active duty soldier was initially admitted to a hospital in Maryland in May 2007 with a 10-day history of intermittent fevers, headaches, rigors, and chills, and a 1-day history of nausea, vomiting, and diffuse abdominal pain. He had been seen elsewhere on two separate occasions, 8 days and 2 days before his admission, for fever and headache. He had been diagnosed as having a viral syndrome and been prescribed acetaminophen. When he subsequently developed abdominal symptoms, he came to the hospital. His symptoms began ~5 months after returning from a 3-year assignment in the Republic of Korea, where he had been stationed near the Demilitarized Zone, and 9 months after participating in field exercises in nearby swampland during which he had received multiple mosquito bites.

On admission, the patient was alert and oriented with a temperature of 103.0°F, heart rate of 124/min, and blood pressure of 93/44 mm/Hg. Physical examination findings were significant for diffuse abdominal tenderness and a petechial rash on the lower extremities bilaterally.

Laboratory studies showed a white blood cell (WBC) count of 2.4×10^9/L, hemoglobin of 13.3 g/dL, and a platelet count of 77×10^9/L. The total bilirubin concentration was 4.9 mg/dL with a direct bilirubin of 1.8 mg/dL. Transaminases were elevated with a serum aspartate aminotransferase (AST) level of 166 U/L, an alanine aminotransferase (ALT) of 108 U/L, and an alkaline phosphatase level of 186 U/L. Examination of a blood thin smear revealed ringed trophozoites typical of the *P. vivax* with 2% of erythrocytes parasitized.

Abdominal ultrasound showed a thickened gallbladder wall (4 mm) and a 6 mm diameter common bile duct, but showed no gallstones or biliary ductal dilatation. A technetium hepatobiliary iminodiacetic acid (Tc-HIDA) scan was abnormal, revealing non-filling of the gallbladder with normal bile transit through the common duct into the small bowel. Acalculous cholecystitis was diagnosed. The surgeon consulted elected not to perform a cholecystectomy because previously reported cases of malaria-related AAC had resolved with medical therapy.

Treatment was begun with oral quinine sulfate, oral doxycycline, and intravenous (IV) fluids. Intravenous levofloxacin and clindamycin were also started before the peripheral smear was obtained because of concern for intra-abdominal bacterial infection.

Over 3 days after initiation of antimicrobial therapy, the patient's clinical condition improved. Levofloxacin and clindamycin were discontinued after the patient's fever resolved. By Day 6 his serum ALT and AST, though still mildly elevated, had declined. His serum alkaline phosphatase and total bilirubin levels, and his WBC and platelet counts returned within normal limits. A repeat blood smear on Day 5 of treatment showed clearance of parasitemia. His hemoglobin concentration, however, trended down to 8.5 g/dL by Day 4 before it began to climb. His clinical symptoms resolved completely by Day 6. The patient was discharged with instructions to complete a 2-week course of primaquine. Ultrasonography of the abdominal right upper quadrant (RUQ) 2 months after hospital discharge showed complete resolution of the cholecystitis.

CASE REPORT 2

A 21-year-old male, Caucasian, active duty army Ranger was admitted to a hospital in Georgia in June 2003 with a 7-day history of intermittent fevers, rigors, and acute mental status changes. The symptoms appeared ~1 month after returning from a 3-month deployment to Iraq and 8 months after serving in Afghanistan from June to September 2002. The patient had received weekly mefloquine for malaria prophylaxis while stationed in Afghanistan, and daily doxycycline for prophylaxis while in Iraq. After returning to the United States, he took ~7 days of a prescribed 14-day course of primaquine for terminal prophylaxis and did not receive blood stage prophylaxis.

On admission, the patient was somnolent and oriented only to person. His temperature was 103.5°F and his heart rate was 134/min. Physical examination did not reveal any abdominal tenderness, rashes, jaundice, neck stiffness, or focal neurological signs.

Laboratory studies showed a WBC of 3.8×10^9/L, hemoglobin of 9.9 g/dL, and a platelet count of 33×10^9/L. His serum total bilirubin concentration was 2.6 mg/dL; direct bilirubin concentration was 0.8 mg/dL. Serum transaminase levels were normal

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with an AST level of 28 U/L and ALT of 14 U/L. The serum alkaline phosphatase level was normal at 58 U/L. Initial blood thick and thin smears revealed *P. vivax,* but because of concern for a mixed infection, treatment was begun with oral chloroquine, oral primaquine, oral doxycycline, and oral mefloquine. Repeat blood thick and thin smears after 24 hours confirmed ring trophozoites typical of *P. vivax*, with 5% of erythrocytes parasitized. Both sets of slides were reviewed with pathologists and infectious disease specialists who agreed with this diagnosis. Within 24 hours, the patient became hypotensive and hypoxic. His chest x-ray then showed patchy bilateral infiltrates. His antimalarial therapy was changed to IV quinidine, IV doxycycline, and oral primaquine for 3, 7, and 14 days, respectively. Piperacillin/tazobactam and levofloxacin were added empirically, but were discontinued after repeat blood, urine, and sputum cultures were negative, before he developed AAC.

After the initiation of antibiotic therapy, over the next 2 days, his clinical condition worsened. He required fluid resuscitation, vasopressor support, and endotracheal intubation with ventilator support on hospital Day 2 for acute respiratory distress syndrome. Soon after intubation he was started on stress dose corticosteroid therapy, and treated with recombinant human activated protein C at 24 μg/hr for 96 hours. Bacterial cultures of blood, bone marrow, and bronchial alveolar lavage fluid were all negative. On hospital Day 5 the patient underwent a computerized automated tomography scan of the abdomen that showed no biliary ductal dilatation and a patulous gallbladder without inflammatory changes. The patient continued to have a complicated hospital course and by Day 9 began to complain of RUQ abdominal pain. Laboratory tests at that time showed a serum total bilirubin level of 1.4 mg/dL, direct bilirubin of 0.6 mg/dL, AST of 60 U/L, ALT of 28 U/L, and alkaline phosphatase of 219 U/L.

On hospital Day 10 an abdominal ultrasound revealed a thickened gallbladder wall (4.5 mm) and a 7 mm common bile duct, but no evidence of stones or biliary ductal dilatation. A Tc-HIDA scan was abnormal, revealing a nonfunctional cystic duct and no evidence of common duct obstruction. Acalculous cholecystitis was diagnosed. On Day 11 the patient underwent successful placement of a percutaneous transhepatic cholecystostomy tube and received a single dose of piperacillin/tazobactam. After placement of the drain, his symptoms related to the RUQ pain improved. By Day 13, his AST, ALT, total bilirubin, and direct bilirubin serum levels had all declined to normal levels, and his serum alkaline phosphatase level had declined to near normal at 131 U/L.

The patient's symptoms related to AAC continued to improve. On Day 24, he underwent an antegrade cholecystogram through the cholecystostomy tube that showed a patent cystic duct with antegrade flow into the duodenum. The tube was subsequently capped, and then 4 weeks later removed without complication. He eventually recovered and was discharged after a hospital stay of 10 weeks. He suffered two relapses of *P. vivax* over the next 3 months, with species confirmation by both microscopic examination and polymerase chain reaction (PCR).[1]

DISCUSSION

Acalculous cholecystitis is a syndrome of gallbladder inflammation without gallstones. Most patients who develop AAC will have had no prior history of gallbladder disease.[2] The syndrome is most commonly recognized within the setting of some physiological insult, e.g., trauma, surgery, burns, or sepsis,[3] but more recent studies have suggested that AAC may occur without an identifiable precipitant.[4] Alertness to possibility of AAC is important, because clinical findings are variable and nonspecific.[5] Although most patients with AAC will have RUQ abdominal pain, 15–44% of patients with AAC have been reported to lack localized abdominal pain. Fever may be absent more often than not. Routine laboratory testing shows elevated serum transaminase levels in about 40% of cases, elevated alkaline phosphatase levels in about half of cases, and elevated serum bilirubin levels in about two-thirds of cases. Leukocytosis is typical, occurring in about 75% of cases[2,6]; almost all of these findings, even when present, may be attributed to the primary condition that precipitated AAC. Diagnostic imaging of the gallbladder is essential in establishing the diagnosis of AAC. Either sonography or computed tomography that demonstrates pericholecystic fluid or > 4 mm thickening of the gallbladder wall in the absence of hypoalbuminemia or ascites is strongly suggestive of AAC.[7] Hepatobiliary scintigraphy is highly sensitive for detecting AAC, but it is nonspecific. Such scanning is more useful for excluding the diagnosis than for confirming it. Morphine augmentation can enhance the specificity of scintigraphy.[8] Establishing the diagnosis of AAC as early as possible is important, because delay in treatment is associated with high risk for gallbladder perforation or gangrene.[2,6] The recommended treatment of AAC is immediate hemodynamic stabilization and initiation of broad spectrum antibiotics providing coverage for enterococci, Gram-negative bacilli, and anaerobes,[3] followed by prompt percutaneous cholecystostomy.[5,9] Cholecystectomy may be required in the 10–15% of cases in which cholecystostomy does not result in adequate improvement.

In this report, we describe the first two cases of AAC as a complication of *P. vivax* malaria infection in adults. The AAC as a syndrome, first described in 1947 and distinguished in 1962,[10] has in the last 20 years been recognized in at least 11 cases of *P. falciparum* malaria and one case of *P. vivax* malaria in a child (see Table 1). Another case described AAC in the setting of a mixed infection with *P. falciparum* and *P. vivax*.[22] A second case reported as mixed infection with *P. falciparum* and *P. vivax* was also associated with AAC, but several features of that second report strongly suggest that *P. vivax* was misdiagnosed, and that the infection was either pure *P. falciparum* or, less likely but possibly given its locale, a mixed infection with *P. falciparum* and *P. ovale*.[23] The acquisition of this infection in Nigeria, and the initial 10% parasitemia weigh against *P. vivax* as the infecting species. Nigerians, like most West Africans, typically lack red blood cell Duffy receptors required to contract *P. vivax*. In addition, *P. vivax* infects reticulocytes, and therefore rarely exceeds 5% parasitemia.[24,25] *Plasmodium ovale*, like *P. vivax*, infects reticulocytes, and should, likewise, fail to generate such intense parasitemia. In the absence of other supporting diagnostic data such as PCR or a rapid test, both the location of the exposure and the high level of parasitemia suggest that this patient was very unlikely to have been infected with *P. vivax*.

The AAC was an unexpected complication in all of these cases and the resultant morbidity was severe in three of the patients, with two requiring placement of a cholecystostomy tube. Mortality was avoided in all cases, but questions

TABLE 1
Cases of AAC in *Plasmodium vivax* and *Plasmodium falciparum**

Variables	*Plasmodium vivax*			*Plasmodium falciparum*			
	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
Age (years)	9	26	21	42	42	26	24
Gender	Male	Male	Male	Male	Female	Female	Female
Race/ethnicity	Unknown/ South Asian	Caucasian	Caucasian	Unknown/ Venezuelan	Unknown/reunion (Indian Ocean)	African (Togo)	Caucasian (Spanish)
Admission							
Temp (Fahrenheit)	Not reported	103.0	103.5	Febrile, not specified	Febrile, not specified	103.1	102.2
Pulse rate (beats/ minute)	110	124	134	Not reported	Not reported	120	105
Blood Pressure (mm/Hg)	Systolic 76	93/44	mean arterial pressure < 50	Not reported	Not reported	80/35	90/50
RUQ Abdominal pain-l present/not present (±)	(+)	(+)	(−)	Not reported	Not reported	(+)	(+)
WBC (per Liter)	4.0×10^9	2.4×10^9	3.8×10^9	Not reported	Not reported	4.5×10^9	6.2×10^9
Hemoglobin (grams/ deciliter)	10	13.3	9.9	Not reported	8.9	10.4	8.9
Platelet count (per Liter)	60×10^9	77×10^9	33×10^9	Not reported	15×10^9	56×10^9	11×10^9
Blood thin smear % parasitemia	*P. vivax*, not quantified	*P. vivax*, 2%	*P. vivax*, 5%	*P. falciparum*, not quantified	*P. falciparum*, 15% parasitemia	*P. falciparum*, not quantified	*P. falciparum*, not quantified
Malaria rapid diagnostic test-*Plasmodium falciparum* histidine-rich protein-2 (HRP2) and parasite lactate dehydrogenase (pLDH) positive test (+)	Not performed	Not performed	Not performed	Not performed	Not performed	Not performed	Not reported but *P. falciparum* serology (+)
Polymerase chain reaction (PCR)	Not performed	Not performed	*P. vivax*, relapse only	Not performed	Not performed	Not performed	Not performed
Studies at time of AAC							
Total bilirubin (milligrams/deciliter)	Not reported	4.9	1.4	12	4.6	3.5	6.9
Direct bilirubin (milligrams/deciliter)	Not reported	1.8	0.6	8	2.5	0.5	6.5
AST (U/liter)	Not reported	166	60	76	Not reported	Reported within normal limits	214
ALT (U/Liter)	Not reported	108	28	Not reported	Not reported	Reported within normal limits	254
Alk phosp (U/Liter)	Not reported	186	219	Not reported	Not reported	Reported within normal limits	423
Abdominal ultrasound							
Gallbladder wall (millimeters)	Thickening, not quantified	4	4.5	13	Not performed	5	Thickening, not quantified
Common bile duct (millimeters)	Not reported	6	7	Not reported	Not performed	Not reported	Not reported
Stones-present/ not present (±)	Not reported	(−)	(−)	Not reported	Not performed	(×)	(−)
Biliary ductal dilatation-present/ not present (±)	Not reported	(−)	(−)	Not reported	Not performed	Not reported	Not reported
Pericholecystic fluid-present/ not present (±)	(+)	Not reported	Not reported	Not reported	Not performed	(+)	(+)

TABLE 1
Continued

Plasmodium falciparum							Mixed *P. vivax*/ *P. falciparum*	Reported mixed *P. vivax*/ *P. falciparum*
Case 8	Case 9	Case 10	Case 11	Case 12	Case 13	Case 14	Case 15	Case 16
47 Male African (Nigerian)	7 Female Unknown/ South Asian	24 Female African (Cameroon)	7 Female Not reported	8 Male Unknown/ South Asian	3 Female South Asian	26 Female Unknown/ Spanish	40 Male African/ Eritrean	46 Female Caucasian
99.5	102.2	103.1	99.1	Febrile, not specified	102.2	101.8	103.1	102.2
102	150	118	102	120	120	Not reported	118	Not reported
108/62	Not reported	95/50	111/66	systolic 80	96/60	95/65	100/60	100/60
Not reported	(+)	(+)	(+)	(+)	(+)	(+)	(+)	Not reported
4.8×10^9 12.2	7.2×10^9 8	4.1×10^9 10.7	11.8×10^9 7.9	6.0×10^9 6	14.1×10^9 5.4	6.1×10^9 12.9	7.9×10^9 10.4	$5. \times 10^9$ 13.4
55×10^9	Not reported	38×10^9	102×10^9	18×10^9	56×10^9	49×10^9	84×10^9	27×10^9
P. falciparum, 0.03% rising to 6.6% parasitemia	*P. falciparum*, not quantified	*P. falciparum*, 6% parasitemia	Negative	*P. falciparum*, not quantified	*P. falciparum*, not quantified as %	*P. falciparum*, 4% parasitemia	*P. falciparum*/ *P. vivax* not quantified	Reported 30% *P. falciparum*/ 10% *P. vivax*
(+) HRP2/ aldolase	(+), unspecified assay	Not performed	*P. falciparum* (+), unspecified assay	(+) HRP2/ pLDH	(+) HRP2	Not performed	Not performed	Not performed
Not performed	Not performed	Not performed	Not reported	Not performed	Not performed Unspecified liver function tests within normal limits	Not performed pre-AAC values; not reported at time of AAC	Not performed	Not performed
1.0	Not reported	1.5	17.2	Reported within normal limits	Not reported	5.7	2.3	1.5
Not reported	Not reported	0.5	14.4	Reported within normal limits	Not reported	4.4	Not reported	Not reported
61	Reported within normal limits	50	74	97	Not reported	129	120	59
25	Reported within normal limits	70	111	Reported within normal limits	Not reported	Not reported	95	80
182	Reported within normal limits	Not reported	Not reported	Reported within normal limits	Not reported	Not reported	122	Not reported
Not performed	Thickening, not quantified	10	5	Thickening, not quantified	6	Thickening, not quantified	6	5
Not performed	Not reported	Not reported	Normal	Not reported	Not reported	Not reported	Reported as not distended	Reported within normal limits
Not performed	(−)	(−)	(−)	(−)	(−)	(−)	Not reported	(−)
Not performed	Not reported	Not reported	(−)	Not reported	Not reported	Not reported	(−)	(−)
Not performed	(+)	Not reported	Not reported	(+)	Not reported	(+)	(+)	(+)

(Continued)

TABLE 1
Continued

Variables	*Plasmodium vivax*			*Plasmodium falciparum*			
	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
HIDA scan Findings	Not performed	Impaired filling with normal bile transit through the common duct into small bowel	Impaired filling	Not performed	Not performed	Not performed	Not performed
Malaria treatment	Quinine	Quinine sulfate Doxycycline	Chloroquine Primaquine Quinidine Doxycycline Mefloquine	Yes, unspecified	Quinine	Quinine Doxycycline	Quinine Doxycycline
Antibiotic treatment	Not reported	Levofloxacin clindamycin (and doxycycline)	Piperacillin-tazobactam, Levofloxacin	Not reported	Yes, unspecified	Yes, unspecified (and doxycycline)	Ceftriaxone metronidazole (and doxycycline)
Surgical intervention (yes/no)	No	No	Yes (cholecystostomy tube)	No	Yes (cholecystostomy tube)	No	No
Severity of illness (critical/not)	Not critical	Not critical	Critical	Not critical	Critical	Not critical	Not critical
Outcome	Cure	Cure	Cure	Cure	Cure	Cure	Cure
Author and Date	Kuttiat, 2007†	Curley, 2011	Curley, 2011	Garassini, 1989‡	Gaüzère, 1998§	Dylewski, 1999¶	Sanchez, 2000⊥

*RUQ = right upper quadrant; WBC = white blood cell; AAC = acalculous cholecystitis; AST = aspartate aminotransferase; ALT = alanine aminotransferase; HIDA = hepatobiliary iminodiacetic acid.
† Data from Kuttiat, Kohli.[11]
‡ Data from Garassini, Alvarado, Lara.[12]
§ Data from Gaüzère, Roblin, Blanc.[13]
¶ Data from Dylewski, Al-Azragi.[14]
⊥ Data from Sanchez, Portilla, Boix.[15]
** Data from Yasuoka, Yasuoka, Yamamoto.[16]
†† Data from Saha, Batra, Vilhekar.[17]
‡‡ Data from Yombi, Meuris, Van Gompel.[18]
§§ Data from Anthoine-Milhomme, Chappuy, Cheron.[19]
¶¶ Data from Kumar, Taksande, Vilhekar.[20]
⊥⊥ Data from Salinas, Puerta, Olmedo.[21]
*** Data from Khan, El-Hiday.[22]
††† Data from Maggi, Coppola, Lamargese.[23]

regarding the disease process and the proper clinical management of these patients have been raised and remain largely unanswered.

Although AAC is commonly defined as an inflammation of the gallbladder without evidence of gallstones,[10] it might be better termed necrotizing or ischemic cholecystitis based on proposed etiologies and available pathologic findings.[26] Gallbladder ischemia, hemodynamic instability, systemic infections, bile stasis, and the use of total parenteral nutrition in prolonged fasting states[3] have all been found in association with AAC, so many of these processes have been studied to find a common denominator in the pathogenesis of AAC. Because a majority of these states often occur in complex, critically ill individuals, the exact pathogenic mechanisms remain at best only partially elucidated, and any link to malaria has been to date poorly understood. Despite these difficulties, an exploration of these proposed mechanisms provides a starting point for discussion on how malaria ties in to AAC, and may contribute to a more thorough understanding of any similarities or differences between AAC caused by *P. vivax* or *P. falciparum infection*.

One proposed mechanism to explain the pathogenesis of *P. falciparum* mediated AAC is an extension of a well-described disease process in *P. falciparum* infection termed sequestration.[17,18] During this process, infected erythrocytes aggregate bind each other and adhere to vessel walls, causing diffuse vascular sludging and ischemia. This is an attractive explanation in *P. falciparum* AAC because AAC alone is often linked to ischemic precipitants, but it fails to explain the process of *P. vivax*-mediated AAC. Sequestration depends on a protein specific to *P. falciparum* that forms "knobs" on the cell membranes of infected erythrocytes.[27] *Plasmodium vivax* does not produce this protein, does not form "knobs," and has not been found to be linked with sequestration,[28,29] making this an extremely unlikely explanation for *P. vivax*-associated AAC. *Plasmodium vivax* does, however, exhibit a cytoadherence phenomenon in which infected erythrocytes bind endothelial receptors in a similar fashion to *P. falciparum*.[30] This recent

TABLE 1
Continued

Plasmodium falciparum							Mixed *P. vivax*/ *P. falciparum*	Reported mixed *P. vivax*/ *P. falciparum*
Case 8	Case 9	Case 10	Case 11	Case 12	Case 13	Case 14	Case 15	Case 16
Not performed	Not performed	Not performed	Not performed	Not performed	Not performed	Not performed	Not performed	Not performed
Mefloquine Artesunate	Quinine	Quinine Doxycycline Clindamycin Atovaquone/ proguanil	Halofantrine	Quinine	Artesunate	Quinine Doxycycline	Quinine Doxycycline	Chloroquine phosphate Quinine chlorhydrate Clindamycin
Ceftazidime	Ceftriaxone	Cefuroxime metronidazole (and doxycycline)	Thiamphenicol amoxicillin	Ceftriaxone	Yes, unspecified	None other than doxycycline	None other than doxycycline	Ceftriaxone ciprofloxacin clindamycin
No	No	No	No	No	No	No	No	No
Not critical	Not critical	Not critical	Not critical	Not critical	Not critical	Not critical	Not critical	Critical
Cure Yasuoka, 2001**	Cure Saha, 2005††	Cure Yombi, 2006‡‡	Cure Anthoine-Milhomme, 2007§§	Cure Kuttiat, 2007†	Cure Kumar, 2008¶¶	Cure Salinas, 2009⊥⊥	Cure Khan, 2009***	Cure Maggi, 2002†††

discovery has been implicated as a possible mechanism in the pathogenesis of *P. vivax* malaria, and could potentially play a role in *P. vivax* associated AAC.

Another very plausible theory for malarial AAC, consistent with *P. vivax,* is oxygen demand-related ischemia and reperfusion injury. Ischemia is thought to play a prominent role in AAC, and gallbladder microangiopathic findings from patients with AAC secondary to shock are consistent with microcirculatory insufficiencies not seen in cases of gallstone-mediated acute cholecystitis.[26] This suggests that the low flow states often seen in association with AAC may help explain the pathogenesis of malaria-mediated AAC. In addition, malarial infections often cause hemolytic anemia, which, either alone or in conjunction with low flow states, predisposes patients to multifactorial demand ischemia. A major flaw with this theory, however, is that many of the patients with malaria-induced AAC were not critically ill and did not manifest a low flow state. It is possible that a combination of hypoperfusion and hemolysis was to blame, especially since most patients manifested both characteristics in varying proportions, but this is not entirely clear.

A third mechanism that may play either a primary or secondary role, and also accounts for both forms of malaria-related AAC, is the imbalance of pro-inflammatory and anti-inflammatory cytokines that occurs during malarial infections. Both *P. vivax* and *P. falciparum* have been shown to induce the cytokines IL-6, IL-10, IL-12, and TNF-α during acute infections,[31–33] setting the stage for systemic inflammatory responses that may incite or exacerbate gallbladder injury.

Further clues to the pathogenesis, as well as the proper management, of AAC in malaria patients may lie in the two cases presented in this report. Before these cases, there was little evidence that AAC occurred in the setting of *P. vivax*, with almost all of the cases citing *P. falciparum* as the offending agent. These two cases of adult *P. vivax* AAC provide the first complete comparisons to cases of *P. falciparum*-mediated AAC and generate intriguing questions regarding the understanding of AAC complicated malaria. They may have broad implications as well, because *P. vivax*, although classically considered to be a less serious cause of malaria, has in recent years been implicated as a more frequent cause of severe, complicated, malarial illness.[29,34,35] These observations are concerning because there may be an inappropriately low clinical suspicion for severe complications such as AAC-associated with *P. vivax* malaria, thus leading to dampened provider vigilance, delayed diagnosis, and worsened overall outcomes.

In the first presented case, the patient developed manifestations of *P. vivax* malaria ~9 months following exposure in Korean swampland. Because his exposure was isolated to the Korean peninsula, he could only have contracted "temperate climate" *P. vivax*, the only type of malaria endemic there.

This patient was not critically ill, but developed AAC anyway. This stands in stark contrast to the second case presented here, in which the patient developed AAC in the context of severe illness. This observation highlights the fact that this serious complication can develop with or without other severe comorbid precipitants of AAC. The course of the illness of the first patient did not seem to differ significantly in many aspects

of his presentation when compared with 10 previous cases of uncomplicated (non-critically ill) *P. falciparum*-related AAC and the one case of *P. vivax*-related AAC in a child. Presenting symptoms were generally consistent, including nausea, vomiting, and abdominal pain in the context of normal to mild laboratory abnormalities. Vital signs were often consistent, with tachycardia, lower than average blood pressures, and fevers being typical. Ultrasonography findings were, when reported, consistent with a thickening of the gallbladder wall (4–13 mm) and all of the symptoms resolved with medical treatment of the malaria.

Notable features in the first presented case of *P. vivax* did include a less severe parasitemia, with only 2% of erythrocytes parasitized as opposed to 6–30% in the cases of *P. falciparum*.

The patient discussed as our first case was successfully treated with medical therapy alone. Oral quinine sulfate and doxycycline were chosen for the initial treatment regimen. The Infectious Disease Service was consulted on hospital Day 5 and chose not to substitute the usual antimalarial treatment choice for *P. vivax,* chloroquine, because significant improvement occurred with the initial regimen. Successful medical management in this patient did not contrast with other uncomplicated patients, including the child with *P. vivax*. Most regimens used to treat these patients (all but two) used some form of quinine in the treatment. Of the 13 uncomplicated patients, none required surgical intervention.

In the second case reported here, there were many contrasts from the presentations of the *P. falciparum* cases, and from our first case of adult *P. vivax*. The patient contracted *P. vivax* in either Iraq or Afghanistan, and the infecting *P. vivax* strain later caused repeated relapses after multiple courses of primaquine, 30 mg twice daily. Presenting symptoms were quite severe and included acute mental status changes with the lowest blood pressures, highest fevers, and most medication changes observed in any of the recorded cases. Unlike the other cases, this patient developed RUQ pain almost 9 days after the initial presentation, whereas most of the others developed RUQ pain 1 to 3 days after presentation. When compared solely to the other adult case of *P. vivax*, this patient manifested a much higher percentage of erythrocytes parasitized, 5%. This is generally considered to be a very significant parasite load for *P. vivax,* but PCR conducted upon relapse did confirm *P. vivax* infection. This was one of only two reported cases that required surgical intervention with cholecystostomy tube placement, the most serious complication from malaria-related AAC yet reported. Surgery achieved definitive cure in both cases where it was used, one *P. vivax* and the other *P. falciparum*.[13] A third case of *P. falciparum*-related AAC (likely misdiagnosed *P. falciparum* and *P. vivax*) was considered critical in severity, but unlike the other two severe cases mentioned medical management sufficed.[23]

Of all 16 cases of AAC-related malaria, three were critically ill and 13 were not. Eleven of the patients (both complicated and non-complicated), received concomitant antibiotic therapy in addition to antimalarial therapy when the AAC developed. There did not appear to be a clear difference in outcomes between complicated and non-complicated patients associated with additional antibiotic therapy when AAC began. None of the non-complicated (non-critically ill) patients required surgery, suggesting less urgency for establishing the diagnosis of AAC in either the vivax or falciparum cases so long as they were not critically ill. These patients seemed to all recover without sequelae after appropriate medical treatment of their malaria. Thus, in these cases, it appears safe to treat medically and avoid surgical interventions. In the three complicated patients, however, cholecystostomy placement was required twice, thus increasing the urgency of establishing a diagnosis. In patients with malaria, regardless of the species of malaria that is diagnosed, elevated transaminases, alkaline phosphatase, and bilirubin, especially when accompanied by RUQ pain or tenderness, should prompt a diagnostic evaluation to exclude AAC, because treatment will be altered if these signs are caused by AAC rather than malaria alone.

None of the critical or non-critical patients required cholecystectomy. If, however, the patient's clinical status deteriorates in the setting of liver-associated enzyme increases, surgical intervention may be indicated, and cholecystostomy may be acceptable as the initial procedure.

Received December 23, 2010. Accepted for publication April 15, 2011.

Acknowledgment: The American Committee on Clinical Tropical Medicine and Travelers' Health (ACCTMTH) assisted with publication expenses.

Disclaimer: The views expressed in this article are those of the authors and do not reflect the official policy of the Department of the Army, Department of Defense, or U.S. Government.

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