A case of acute interstitial nephritis and granulomatous hepatitis induced by ingesting quinine

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Abstract Quinine is used for the treatment of malarial infection, though not in common use. It is especially valuable for the parenteral treatment of severe illness owing to drug-resistant strains of *Plasmodium falciparum*. Quinine is also known to occasionally cause acute renal failure (ARF). Although quinine is listed in some reviews as a cause of acute interstitial nephritis, most cases of quinine-associated acute renal failure have been attributed to the hemolytic-uremic syndrome (HUS). Only two cases of acute renal failure due to acute interstitial nephritis associated with quinine have been reported [1, 2]. To our knowledge, there have been 6 reported cases of quinine-induced hepatic granuloma [3–8]. We report a case of quinine-induced acute interstitial nephritis (AIN) along with granulomatous hepatitis, both of which were confirmed on biopsy. A 50-year-old Nigerian man was admitted to the hospital with complaints of fever and general fatigue. He had been prescribed quinine as an antimalarial drug in a Nigerian hospital. The patient was febrile and showed nonoliguric ARF and liver dysfunction. In this case, liver injury showed gradual and spontaneous resolution after discontinuing quinine, and ARF resolved after treatment with oral prednisolone.

Keywords Acute interstitial nephritis · Hepatic granuloma · Quinine · Biopsy · Acute renal failure

Introduction

Preferred regimen for treatment of infection with *P. vivax*, *P. malariae*, *P. ovale*, and chloroquine-sensitive *P. falciparum* is Chloroquine phosphate in recent years. Quinine is more toxic and less effective than chloroquine against malarial parasites susceptible to both drugs. However, quinine, along with its stereoisomer quinidine, is especially valuable for the parenteral treatment of severe illness owing to drug-resistant strains of *P. falciparum*, even though these strains have become more resistant to both agents in certain parts of Southeast Asia and South America [9].

Quinine, a natural major alkaloid derived from the bark of the cinchona tree, was once mainly used for treating malaria. Possible side effects associated with the use of quinine include hypersensitivity reactions, cinchonism, impaired vision, gastrointestinal symptoms, thrombocytopenia, cardiovascular effects, and hypoglycemia. Only two cases of quinine-associated ARF due to acute interstitial nephritis (AIN) have been reported to date [1, 2], although most cases of quinine-induced acute renal failure have been attributed to thrombotic thrombocytopenic purpura-hemolytic uremic syndrome (TTP-HUS) [10]. On the other hand, quinine-induced granuloma hepatitis has been confirmed and reported in 5 cases [3–8]. We report a rare case of a Nigerian man who developed ARF and acute liver injury after taking quinine. Liver biopsy showed intralobular epithelioid cell granulomas, and renal biopsy showed AIN. To the best of our knowledge, this represents the first description of biopsy-confirmed AIN along with granulomatous hepatitis caused by quinine toxicity.

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Case report

A 50-year-old Nigerian man was admitted to our hospital for the investigation of fever, general fatigue, and anorexia. He had gone back to Nigeria 2 months earlier. He had been prescribed quinine as an antimalarial in a Nigerian hospital when he presented with fever and general fatigue, 3 weeks before presenting to our hospital. A diagnosis of malaria was not confirmed, and the exact dose and period of quinine administration were also obscure. After taking quinine, fever had improved for a short time, but recurred several days later. He started experiencing malaise and loss of appetite after arriving in Japan 1 week before visiting our hospital. He had suffered from malaria several times previously. He denied taking any medications other than quinine, and had no history of drug or food allergies. He had not taken any illicit drugs, had not received blood transfusions and had not consumed any significant amount of alcohol. He was a well-built man, 181 cm tall and weighing 90 kg.

On admission, the patient appeared ill and was febrile, with a temperature of 39.1 °C. Blood pressure was 138/88 mmHg, and heart rate was 80 beats/min. He was slightly anemic, but not jaundiced, and neither skin eruptions nor lymphadenopathy were evident.

A complete blood cell count showed: white blood cell count, 7,010/ μ l; hemoglobin, 10.8 g/dl; platelets, 2.53×10^5 / μ l, without schizocytes. Serum chemistry showed: albumin, 2.7 g/dl; blood urea nitrogen, 39.4 mg/dl;

creatinine, 6.53 mg/dl; blood glucose, 98 mg/dl; and C-reactive protein, 6.12 mg/dl. Liver function tests showed: total bilirubin, 1.3 mg/dl; aspartate aminotransferase, 150 U/l; alanine aminotransferase, 216 U/l; alkaline phosphatase, 1,742 U/l; and γ -glutamyl transpeptidase, 593 U/l. Urinalysis revealed: protein 2+; blood $\pm$; granular casts 2+; epithelial casts 1+; and tubular epithelium. Fractional excretion of sodium was 4.5 % (Table 1).

Malaria was immediately excluded based on the rapid diagnostic test and microscopy. No evidence of recent infection with hepatitis A, B, or C viruses, Epstein–Barr virus, cytomegalovirus, or human immunodeficiency virus was found. Blood, sputum, urine, and fecal cultures all yielded negative results, and there was no evidence of active tuberculosis. The level of serum angiotensin-converting enzyme was normal and sarcoidosis was considered unlikely. HUS was deniable, since the number of platelets and haptoglobin were normal and a peripheral smear showed no schizocytes.

Ultrasonography of the abdomen showed enlargement of the right lobe of the liver. Renal ultrasonography revealed enlarged kidneys with increased cortical echogenicity. On day 5 of hospitalization, percutaneous needle biopsy of the liver revealed epithelioid cell granuloma and mild neutrophil infiltration in the hepatic lobule (Fig. 1). The granulomas were non-caseating and also seen in the portal area. Q fever was suspected based on the prolonged fever and liver granuloma, but was later excluded based on serological testing. On day 14, fever decreased to 36.0 °C.

Table 1 Laboratory data on admission

CBC		Blood chemistry		Serological tests	
WBC	7,010/ μ l	Total protein	7.8 g/dl	C3	156 mg/dl
Neutro.	68 %	Alb	2.7 g/dl	C4	45.1 mg/dl
Lymph.	25 %	BUN	39.4 mg/dl	Haptoglobin	314.2 mg/dl
Mono.	7 %	Cr	6.53 mg/dl	IgG	2,274.4 mg/dl
Eosino.	0 %	Na	138 mEq/l	IgA	265.8 mg/dl
RBC	5.03×10^6 / μ l	K	4.3 mEq/l	IgM	135.2 mg/dl
Hb	10.8 g/dl	Cl	104 mEq/l	P-ANCA	<1.3 U/ml
Platelets	2.53×10^5 / μ l	Ca	9.3 mg/dl	C-ANCA	<1.3 U/ml
Urinalysis		Glucose	98 mg/dl	ANA	all negative
Protein	2+	CRP	6.12 mg/dl	ACE	20.6 μ g/l
Occult blood	1+	T.Bil	1.1 mg/dl	Binax NOW	(–)
Leucocytes	1–5/HPF	AST	150 U/l	Malaria	
Erythrocytes	1–5/HPF	ALT	216 U/l	Malaria (Giemsa stain)	(–)
Epithelial casts	1+	LDH	319 U/l	Anti-HA IgM	(–)
Urine chemistry		ALP	1,742 U/l	HBs Ag	(–)
Protein	0.49 g/day	γ -GTP	593 U/l	Anti-HCV	(–)
FEUN	64.9 %	ChE	198 U/l	HIV	(–)
FENa	4.5 %				
Urinary β_2 M	7,467 μ g/L				
Urinary NAG	15.7 U/L

Fig. 1 Light microscopic findings of liver biopsy. Epithelioid cell granuloma (arrows) and mild neutrophil infiltration (hematoxylin and eosin stain, ×400)

Fig. 2 Light microscopic findings of renal biopsy. Renal biopsy demonstrates diffuse interstitial inflammatory infiltration actively invading the tubules. Most glomeruli and vessels appear uninvolved (Periodic acid Schiff stain, ×400)

A gradual decline in liver enzymes such as aspartate aminotransferase and alanine aminotransferase was also seen.

After admission, hydration had been continued and creatinine level decreased to 3.45 mg/dl. The cause of renal failure remained unknown, so renal biopsy was performed on day 26. Light microscopic examination of the renal cortex revealed diffuse interstitial inflammatory infiltration comprising lymphocytes, neutrophils, and prominent eosinophils. Interstitial infiltrates were actively invading the tubules (Fig. 2). Most glomeruli

Fig. 3 Clinical course. In this case, ARF resolved gradually after discontinuing quinine

and vessels were uninvolved. No glomeruli were completely sclerotic. No glomerular subendothelial fibrin deposits were consistent with those seen in hemolytic-uremic syndrome (HUS). No granuloma formation was seen. Immunofluorescence was negative for immunoglobulins A, G, and M, and complement component 3. Electron microscopy showed that the patient's glomeruli were normal.

The clinical course of this patient and renal biopsy findings suggested a diagnosis of drug-induced interstitial nephritis associated with quinine administration. Treatment was started with oral prednisolone at 40 mg/day. Three weeks later, creatinine level decreased to 1.88 mg/dl and the dose of prednisolone was tapered by 5 mg weekly (Fig. 3). As of 1 year later, creatinine level had decreased to 1.6 mg/dl.

Discussion

In this case, there were no laboratory findings which suggested malaria, such as hemolysis, jaundice, and thrombocytopenia and we did not detect parasites on Giemsa-stained blood smears by light microscopy. Therefore, we thought we could deny malaria clinically on admission, although it might be possible that the first episode of fever had been due to malaria.

Malaria itself can cause ARF due to certain forms of renal disease, such as acute tubular necrosis (ATN), acute interstitial nephritis (AIN), and glomerulonephritis [11]. Although isolated interstitial nephritis has not been reported in humans, interstitial inflammation is a common histopathologic finding associated with ATN and acute glomerulonephritis [11]. In our case, pathological findings showed isolated interstitial nephritis without ATN and

without acute glomerulonephritis. Thus, we considered ARF was not associated with malaria in the present case.

AIN is characterized by the presence of inflammatory infiltrates and edema within the interstitium, usually associated with acute renal failure. The renal insufficiency typically is unaccompanied by oliguria or the need for dialysis [12]. The main causes of AIN can be grouped as drug-induced, infection-related, idiopathic forms, and AIN associated with sarcoidosis and other systemic diseases. Drug-induced AIN accounts for more than 75 % of biopsy-proven cases [13].

In this case, previous intake of quinine and renal biopsy findings suggested a diagnosis of drug-induced AIN associated with quinine use. The absence of any other infectious disease or systemic disease rendered other diagnoses very unlikely. AIN has been described most commonly in association with antibiotics, non-steroidal anti-inflammatory drugs, and diuretics. Quinine has only rarely been associated with AIN, but is still included on the list of drugs responsible for AIN [14].

Our patient represents the third reported case of AIN occurring after taking quinine [1, 2]. The second reported case showed liver dysfunction without eosinophilia, the same as the present case [2].

A number of reports have described quinine-induced HUS, and many others have described quinine-induced thrombocytopenia [10, 15]. Our patient showed neither thrombocytopenia nor hemolytic anemia, excluding the possibility of quinine-induced HUS as a cause of renal failure.

On the other hand, hepatic granuloma may also occur in the liver in a wide variety of disorders, such as infections, sarcoidosis, primary biliary cirrhosis (PBC), and as an adverse drug reaction [16]. One report found that drug-induced hepatic granuloma accounted for 11 (2.48 %) of 442 cases of biopsy-proven hepatic granuloma [17]. Many drugs have been associated with hepatic granuloma, the most common of which are allopurinol, sulfa drugs, chlorpropamide, and quinidine [18]. Hepatic injury has been reported more commonly with quinidine, the optical isomer of quinine, which generally leads to the development of granulomatous hepatitis [19]. After other common causes of hepatic granuloma such as sarcoidosis had been excluded, drug-induced disorder was considered in the present case because of the history of quinine administration and the pathological features of liver biopsy.

Our search of PubMed revealed 6 reported cases of quinine-induced hepatic granuloma [3–8]. The number of potential cases of the same pathological condition of quinine-induced hepatotoxicity would be increased if cases without liver biopsy were included [20, 21]. Most such cases presented with nonspecific symptoms such as fever, malaise, nausea, arthralgia, and myalgia. Actually, in the

present case, the patient had been temporarily diagnosed with fever of unknown origin until hepatic granuloma and AIN were histopathologically confirmed.

Interestingly, most patients with quinine-induced hepatic granuloma had taken quinine for leg cramp, not for malaria. In a previously reported case of quinine-induced AIN, the patient also ingested quinine for leg cramp, not for malaria [2]. There may be reason to believe that the pharmacokinetics of quinine may change according to the severity of malarial infection [22]. As reviewed by Silamut et al., the high levels of plasma α_1 -acid glycoprotein produced in severe malaria may prevent toxicity by binding to the drug and thereby reducing the free fraction of quinine [23]. Taking this into account, fever in the present case might not have been induced by malaria when quinine was prescribed in Nigeria.

Drug-induced AIN has been suggested to be associated with extrarenal manifestations of hypersensitivity [14]. Drug-induced granulomatous hepatitis is also said to be an immunological disease involving hypersensitivity [17]. The present case showed a relatively long latency (about 2 weeks) between drug exposure and disease onset. This could be compatible with delayed hypersensitivity to quinine, because some delayed reactions to drug allergy begin after weeks of continuous treatment.

The present case might be considered to have involved a drug reaction with eosinophilia and systemic symptoms (DRESS), because the patient showed fever, malaise, internal organ involvement such as hepatic granuloma and interstitial nephritis, relatively long latency after initiation, and long duration after cessation of the causative drug, quinine [24]. However, the absence of skin eruption and eosinophilia in this case is too atypical for DRESS, and that diagnosis would thus be ruled out.

It remains uncertain that what connected both AIN and granulomatous hepatitis in this case. It may be possible that the granulomatous hepatitis was associated with the elevated blood concentration of quinine, which was due to the decreased renal clearance. The additional data and research would be required.

The injury resulting from drug-induced hepatic granuloma is usually transient, without significant sequelae [18]. On the other hand, recovery of renal function is often incomplete following persistent elevation of serum creatinine levels in patients with drug-induced interstitial nephritis [14]. The probability of recovery depends on the duration of kidney injury prior to diagnosis, and ideally this period should be <2 weeks [25]. In a series of 30 patients with AIN, renal prognosis was less favorable when interstitial infiltrates were diffuse and not patchy [26]. A considerable proportion of affected patients (36 %) develop chronic kidney disease (CKD) [27]. Discontinuation of the causative drug is a basic principle of therapy, and

glucocorticoid therapy has been employed in the absence of subsequent improvements in kidney function, although the benefits of immunosuppressive therapy remain controversial, since the available data are conflicting [25].

In the present case, the patient had been administrated oral prednisolone and serum creatinine level decreased finally to 1.6 mg/dl, although the recovery was incomplete and CKD remained. Insufficient improvement of renal function may be caused by persistence of renal failure over 8 weeks at onset and diffuse interstitial infiltrates.

To the best of our knowledge, this represents the first case report of biopsy-confirmed granulomatous hepatitis and concurrent AIN induced by quinine toxicity. The possibility of quinine inducing these diseases should always be kept in mind alongside other well-known side effects, and some delayed reactions can persist for weeks to months, even after stopping the causative medication.

Conflict of interest The authors have declared that no conflict of interest exists.

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