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Case Report

Artemisinin-induced cholestatic liver injury and intrahepatic ductopenia

Joel Thio [1,2,*], Adam Haig[1], Ei Phyu Phyu Swe[1], Paul Nguyen[1], Kayla Tran[3], Madhavi Kasi[1]

[1]Department of Gastroenterology, The Prince Charles Hospital, 627 Rode Road, Brisbane, Queensland 4032, Australia
[2]Faculty of Medicine, University of Queensland, Mayne Medical School, 20 Weightman St, Brisbane, Queensland 4006, Australia
[3]Department of Anatomical Pathology, Pathology Queensland, The Prince Charles Hospital, 627 Rode Road, Brisbane, Queensland 4032, Australia
*Corresponding author. Department of Gastroenterology, The Prince Charles Hospital, 627 Rode Road, Chermside, Brisbane, QLD 4032 Australia.
E-mail: joel_thio@hotmail.com

Abstract

Artemisinin, an ancient Chinese herbal remedy known colloquially as "Qinghao", is now used as treatment for malaria as recommended by the World Health Organisation. There have been few reports of artemisinin-induced liver injury. Most of these instances of hepatotoxicity are reportedly due to prolonged use of herbal remedies containing artemisinin. To our knowledge, we report the first case of intrahepatic ductopenia in a patient with cholestatic liver injury after artemisinin use.

Keywords: artemisinin; chemical and drug induced liver injury; cholestasis; intrahepatic ductopenia

Introduction

Artemisinin, an ancient Chinese herbal remedy known colloquially as "Qinghao", is used as treatment for malaria as recommended by the World Health Organisation [1]. This was discovered in a research project during the malaria epidemic in the Vietnam War, by Tu Youyou winning the Nobel Prize in 2015 for its discovery. Artemisinin-containing products rarely causes acute liver injury [2]. Based on our literature search, there have been six case reports of herbal artemisinin-induced liver injury. Most of these instances of hepatotoxicity are reportedly due to prolonged use of herbal remedies containing artemisinin [2]. To our knowledge, we report the first case of intrahepatic ductopenia with cholestatic liver injury after artemisinin use.

Case report

A 56-year-old male presented with a one-week history of abdominal pain and three days of jaundice, pruritis, and dark urine. His medical history only included hyperlipidaemia and a previous laparoscopic appendicectomy 16 years ago. He had no prior history of liver disease, denied alcohol consumption and recreational drug use, and had no risk factors for viral hepatitis. He denied any regular medications. He saw his General Practitioner (GP) six days prior to hospital presentation with some abdominal pain who commenced him on a course of Cephalexin 500 mg twice daily for a presumed infection, which he only took for two days before cessation. Blood tests including liver chemistry performed by his GP five months prior to this admission were normal. The patient was alert and oriented on examination, with jaundice and mild upper abdominal tenderness. There was no asterixis, and the remainder of the examination was unremarkable with no signs of chronic liver disease.

The patient had taken several over the counter and herbal supplements over the previous six months including artemisinin, N-acetyl cysteine, and magnesium. These were all self-prescribed with the hope of improving his general well-being. He took artemisinin for a total of thirty days beginning five weeks prior to presentation, at a dose of 392 mg twice daily. He ceased it one week prior to presentation at the onset of his abdominal pain. Two months prior, he took and N-acetylcysteine (NAC) and magnesium tablets for approximately one month (Fig. 1). To our knowledge, we know of no association with hepatotoxicity with either of these substances. The patient denied taking any other medications or supplements.

Laboratory tests on admission showed a total bilirubin of 161 μmol/l, alkaline phosphatase (ALP) of 428 U/l, gamma-glutamyl transferase of 648 U/l, alanine aminotransferase (ALT) of 320 U/l, aspartate aminotransferase (AST) of 152 U/l, and international normalised ratio of 1.0. Viral screening for hepatitis A, B, C, E, cytomegalovirus, Epstein–Barr virus, and human immunodeficiency virus were negative. The metabolic screen was normal. Anti-nuclear antibody titres returned at 1:40, speckled, but other autoimmune screens were negative. The total serum globulin was 33 g/l—immunoglobulin subclasses were not performed. Infective screening was negative. Abdominal ultrasound, computer tomography of the abdomen and pelvis and magnetic resonance cholangiopancreatography were otherwise unremarkable except for a contracted gallbladder without evidence of cholelithiasis or choledocholithiasis. Liver core biopsy revealed predominantly portal inflammation with bile duct epithelial injury (Fig. 2) and ductopenia (6 bile ducts identified

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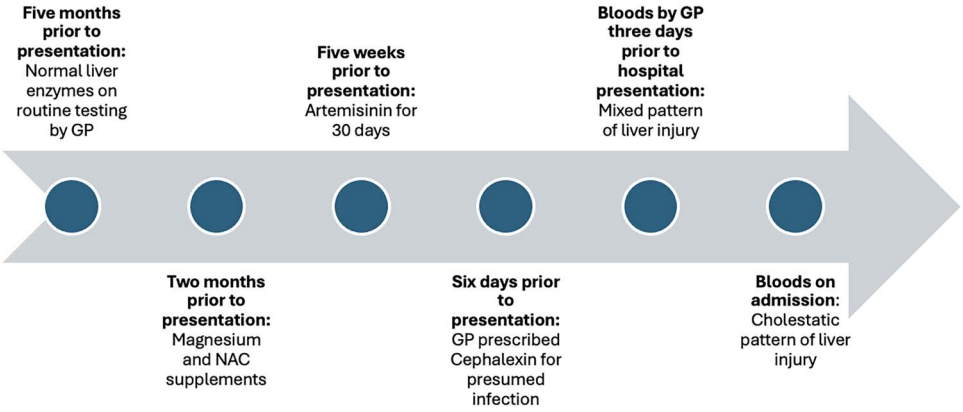

Figure 1. Timeline of medication exposures prior to presentation.

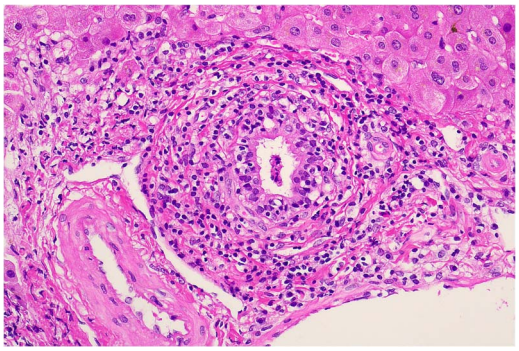

Figure 2. Portal inflammation and bile duct injury with intraepithelial lymphocytes, H&E, intermediate power.

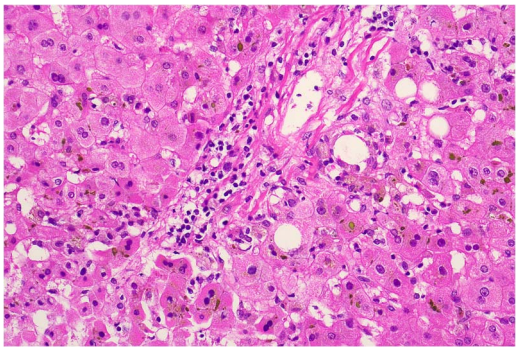

Figure 3. Centrilobular cholestasis and hepatocellular injury, H&E, intermediate power.

out of 18 portal tracts), as well as prominent centrilobular acute cholestasis (Fig. 3).

A diagnosis of artemisinin-induced liver injury was established. Given his pruritis and severe intrahepatic ductopenia, treatment was commenced with antihistamines and Ursodeoxycholic acid. He was monitored with daily blood tests which saw slow improvement in his liver enzymes and bilirubin levels. He was discharged with regular blood tests and is currently under close monitoring (Table 1).

Discussion

Studies show that the use of herbal supplements worldwide has been increasing to about 80% of the world's population [3].

Table 1. Monitoring of liver enzymes over time in our patient

	Bloods with GP	Bloods on admission	+3 weeks	+6 months	+18 months
ALP (U/l)	385	428	415	415	129
ALT (U/l)	431	320	189	168	63
AST (U/l)	180	152	79	65	44
Bilirubin (μmol/l)	89	161	327	17	9

Table 2. RUCAM for Drug-Induced Liver Injury

Category	Points
Time to onset	+1
Course	+2
Risk factors	+1
Concomitant Drugs	-2
Search for non-drug causes	+2
Previous information on hepatotoxicity of the drug	+1
Response to re-administration	0

Artemisinin compounds have been available as an over-the-counter supplement for many years, advertised for use to maintain general health and prevent infections [4]. However, reports of severe liver injury secondary to artemisinin use are very rare [2].

The Roussel Uclaf Causality Assessment Method (RUCAM) is used to assess causality in suspected cases of drug induced liver injury. Using this system, our patient scored 5 points, suggesting artemisinin being a "possible" cause for hepatic injury [5]. The breakdown is shown in Table 2.

The short course of Cephalexin prescribed by his GP reduced the RUCAM score from 7 (probable) to 5 (possible). Evidence suggests that oral Cephalexin is usually associated with only mild, transient elevations in transaminases and alkaline phosphatase values, and not associated with more severe liver injury [6]. In addition, the abdominal discomfort that the patient initially presented to his GP with, for which cephalexin was prescribed, suggests liver injury may have already been present prior to its prescription.

Based on the first set of blood tests done on our patient by his GP, his pattern of hepatic injury was mixed with an R value of 2.85. A subsequent blood test performed on admission three days later

Table 3. Comparing patients from different case reports

	CDC [4]	Kumar [7]	Francisco et al. [8]	Our patient
Artemisinin dose and duration	200 mg three times a day for 10 days	125 mg two-three times a day for six weeks	1250 mg daily for over a month (Estimated 48 g)	392 mg twice daily for 30 days
Latency	Presented 2 weeks after commencement	Presented 6 weeks after commencement	Presented 7 weeks after commencement	Presented 5 weeks after commencement
Liver enzyme values at time of injury	ALP 258 U/l ALT 898 U/l AST 280 U/l Bilirubin 3.1 mg/dl	ALP 208 U/l ALT 675 U/l AST 175 U/l Bilirubin 15.4 mg/dl	ALP 151 U/l ALT 91 U/l AST 42 U/l Bilirubin 186.6 mg/dl	ALP 385 U/l ALT 431 U/l AST 180 U/l Bilirubin 89 mg/dl
Pattern of liver injury at presentation	R 9.48 (hepatocellular)	R = 10.2 (hepatocellular)	R = 1.32 (cholestatic)	R = 2.85 (mixed)
Severity [9]	Grade 3+, moderate to severe	Grade 3+, moderate to severe	Grade 3+, moderate to severe	Grade 3+, moderate to severe
RUCAM	Not calculated	Not calculated	6	5
Time to resolution from presentation	2 weeks	1 year	3 months (reported as normalisation of bilirubin)	6 months (for normalisation of bilirubin)

showed an R value of 1.83, consistent with cholestatic liver injury. We note that Kumar previously described a case of hepatocellular injury secondary to artemisinin use on presentation, followed by the development of cholestatic liver injury [7]. Francisco et al. also reported a similar case, but with a cholestatic pattern of liver injury on presentation, acknowledging that this could be a natural progression of liver injury as in Kumar's patient [8]. Our patient's first set of blood tests with his GP reflected a mixed pattern of liver injury, which then developed into a cholestatic pattern on presentation to the hospital. We hypothesize that our patient presented during the natural progression from a hepatocellular to cholestatic pattern, as previously described by Kumar and Francisco et al. A patient reported by Centres for Disease Control and Prevention (CDC) presented with a hepatocellular pattern of liver injury after two weeks of commencing artemisinin (R value 9.48), which fully resolved after a subsequent two weeks [4]. Table 3 compares patients across the case reports.

Based on our literature search, this is the first reported case of intrahepatic ductopenia secondary to artemisinin use. Kumar and Francisco et al. both conducted liver biopsies on their patients post artemisinin-induced liver injury, both of which showed cholestasis but without evidence of intrahepatic ductopenia.

In summary, we report a severe case of possible artemisinin-induced cholestatic liver injury with severe intrahepatic ductopenia. Given the rare but increasing number of case reports of liver injury associated with artemisinin use at non-recommended doses and frequencies along with the increasing resistances of malaria parasites to artemisinins, we suggest further efforts to control the use of these medicinal compounds [10]. Furthermore, more studies are warranted to understand the predisposition and progression of liver injury in individuals who use artemisinin-based compounds.

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Conflict of interest

No conflicts of interest.

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Ethical approval

The Prince Charles Hospital Human Research Ethic Committee has confirmed that this case report is compliant with the National Statement on Ethical Conduct in Human Research guidelines.

Consent

The patient provided his written consent to participate in this case report.

Guarantor

Joel Thio.

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