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Case Report

CASE REPORT

Azithromycin-induced cholestatic hepatitis

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Abstract

Since its introduction >20 years ago, Azithromycin has been widely used owing to its broad spectrum and good tolerability, especially when used for <7 days. In literature, there are only very few, sporadic reports available of patients developing cholestatic hepatitis following treatment with it. The current case study describes a 69-year old patient, with a medical history that included significant alcohol consumption, who presented with jaundice following a 3-day course of Azithromycin. Following a transjugular liver biopsy, he was managed with a short course of corticosteroids and his liver function gradually improved and finally normalized ~2 months after discontinuation of Azithromycin.

INTRODUCTION

Several drugs, supplements and herbs are implicated in induced liver dysfunction [1], a condition known as drug-induced liver injury (DILI). Presentation varies, mimicking the whole spectrum of liver disease from asymptomatic elevation of liver enzymes to fulminant hepatitis and liver cirrhosis [2]. Antimicrobial agents represent a significant proportion of these cases; Erythromycin in particular is well known to induce hepatotoxixity [3]. The Erythromycin semisynthetic derivative Azithromycin was introduced >20 years ago and since then has been widely used, owing its widespread use to its efficacy and good tolerability [4]. It commonly causes gastrointestinal side effects and has also been implicated in cardiovascular adverse incidents. Conversely, only few sporadic cases of Azithromycin-induced hepatototoxicity have been reported to date [5, 6].

The current report presents a 69-year old man with a medical history that included significant alcohol consumption, who presented with jaundice following a course of Azithromycin and in whom the initial biochemical changes were suggestive of acute alcoholic hepatitis.

CASE REPORT

A 69-year old male patient of Italian roots was admitted to The London Clinic in January 2015 with jaundice, pruritus and abnormal liver function tests. The patient had presented to his General Practitioner in December with productive, intractable cough and malaise and was prescribed a 3-day course of Azithromycin 500 mg once a day. Two weeks after initiation of the antibiotic, he presented again with fever, nausea and vomiting. He was then commenced on Amoxicillin, but in <24 h he reported dark urine, pale stools and associated pruritus. Blood tests showed total bilirubin of 210 umol/l, alanine aminotransferase (ALT) 415IU/l, aspartate aminotransferase (AST) 241IU/l, alkaline phosphatase (ALP) 145IU/l, gamma-glutamyl transferase (GGT) 339IU/l, serum albumin 40 g/l and erythrocyte sedimentation rate 95 mm/h. All medications were discontinued and he was referred to a liver specialist. Repeat blood tests showed further elevation in his liver enzymes with total serum bilirubin having risen to 360.7 umol/l. Serology for hepatitis A, B, C and E, Cytomegalovirus and Epstein–Barr viruses were negative. Autoimmune profile was negative apart from weakly positive anti-smooth muscle antibodies (ASMAs) at 1:40. Liver

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ultrasound and magnetic resonance imaging scan demonstrated mild steatosis and a small cyst at the Segment V of the liver of unclear significance. He was then admitted to hospital.

He was overtly jaundiced and was alert and oriented although he reported reversed sleep pattern. He did not have any associated rash or fever. On physical examination, there were no stigmata of chronic liver disease present. The patient's past medical history was remarkable for hypertension and coronary artery disease. He was a non-smoker and was consuming 70–80 units of alcohol weekly for the last 3 years. He was not aware of any drug allergies and has never been exposed to Azitrhomycin before. He was not on any regular medications.

He was managed with oral Prednisolone 40mg per day, Pentoxifylline 400 mg three times daily, Rifaximin 550 mg twice daily, Ciprofloxacin 500 mg twice daily, Lactulose and intravenous Pabrinex, on presumption of acute alcoholic hepatitis. Although serum bilirubin on admission showed a fall, it remained considerably elevated, as did the rest of the liver enzymes (Table 1, Fig. 1). A transjugular liver biopsy was carried out and intact lobular architecture with no significant fibrosis, mild steatosis, lobular cholestasis and florid portal cholangiolitic changes were shown. Borderline granulomatous changes with eosinophilia were also identified. Findings were disproportionate to the mild degree of steatosis. A cholestatic drug reaction superimposed to an alcoholic injury of mild degree was regarded as the most likely diagnosis. Portal wedge pressures and free hepatic vein pressures were measured and were normal.

All medications except steroids were discontinued and Prednisolone was gradually reduced and finally stopped after 6 weeks. His liver function normalized ~2 months after treatment with Azithromycin (Table 1, Fig. 1).

DISCUSSION

Macrolides are well known to induce liver toxicity and more recently sporadic reports associated Azithromycin with hepatotoxicity, especially in patients with pre-existing liver disease according to the DILI Network (DILIN) study [5–8]. Martinez *et al.* conducted a detailed analysis of patients enrolled in the DILIN study and demonstrated evidence of liver injury caused by Azithromycin; the individuals who fulfilled the set criteria were 18, the mean age for the group was 37 years, the majority were females, one was drinking daily and only one out of three reported previous exposure to Azithromycin. The dominating presenting symptom was jaundice and the majority recovered within 2–5 weeks. Most patients presented with a hepatocellular pattern of liver damage and in those, ANA and/or ASMA were

Table 1: Liver function tests from diagnosis to complete remission

	INR	PT (s)	Albumin (g/l)	Bilirubin (umol/l)	ALT (IU/l)	AST (IU/l)	GGT (IU/l)	ALP (IU/l)
7 January 2015			40	210	415	241	339	145
9 January 2015	0.9	10	38	217	357	260	407	349
14 January 2015	1.1	13	38	216	486	400	960	764
16 January 2015	1.21	16	38	360.7	356	237	847	768
20 January 2015	1.15	16	38	121.3	217	122	889	748
23 January 2015	1.09	14	38	91.6	184	90	663	630
26 January 2015			37	69.3	127	54	559	481
11 February 2015			38	35.6	51	26	138	135
25 February 2015			38	20.2	30	23	80	80
30 March 2015			41	20.7	23	24	87	87

INR, international normalized ratio; PT, prothrombine time.

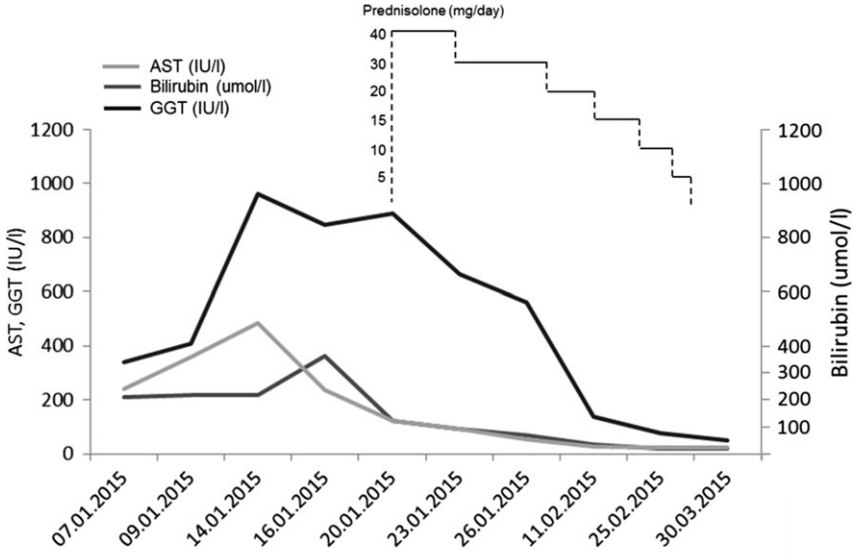

Figure 1: Liver function tests from diagnosis to complete remission in association with Prednisolone.

more likely to be positive. In our case report, the patient only had positive ASMA; the latter is found in only 1 out of 2 individuals with cholestatic injury following treatment with Azithromycin and in none with a mixed pattern of liver injury [9].

The liver injury presented in the current case report is mixed, with the cholestasic pattern dominating. The symptoms began 2 weeks after Azithromycin initiation and took almost 2 months to resolve. The Naranjo *et al.* [10] Adverse Reaction Probability Scale indicated a possible relationship between Azithromycin and liver injury. In most cases published to date, the mean time to onset of symptoms was 17 days and the mean time to recovery 35. There are cases, however, as described by Martinez *et al.* [9] that become chronic, need transplantation or even die.

Considering the patient's initial presentation, suggestive of acute alcoholic hepatitis, the importance of a biopsy cannot be overemphasized, especially in patients with underlying liver disease or those posing a diagnostic challenge. The high level of bilirubin in this patient was likely to have been contributed to by the presence of underlying alcohol-induced liver injury. In the Martinez *et al.* [9] study, there is only one patient with concomitant alcoholic liver disease described, and he is the only one that died following DILI.

In conclusion, the underlying liver disease may influence the course and prognosis of the Azithromycin-induced liver injury, and a biopsy could also show great value in arriving at a diagnosis and subsequently in considering treatment.

CONFLICT OF INTEREST STATEMENT

None declared.

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