Clinical Case Report

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Intrahepatic cholestasis of pregnancy or azithromycin-induced intrahepatic cholestasis

A case report

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Abstract

Rationale: Azithromycin-induced liver injury has been rarely reported in adult individuals, let alone in a pregnant woman. Here, we describe the clinical features and outcomes of azithromycin-induced liver injury in a pregnant woman.

Patient concerns: A 30-year-old pregnant woman presented with generalized pruritus and elevated serum bile acid level (123.6 μmol/L) on day 4 of azithromycin administration. A diagnosis of intrahepatic cholestasis of pregnancy was made, and cesarean section was performed immediately. Interestingly, the alanine aminotransferase level (ALT) reached 211.2 U/L on day 9 after azithromycin administration.

Diagnosis: Therefore, drug-induced intrahepatic cholestasis was considered.

Interventions: (1) Azithromycin withdrawal after the patient hospitalized. (2) Termination of pregnancy by cesarean section was performed inmmediately to protect the fetus. (3) Silymarin capsules and bifendate are used to protect the liver after liver enzymes elevation was discovered.

Outcomes: The liver enzymes recovered within 4 weeks without any symptoms after treatment with silymarin capsules and bifendate, which helps reduce ALT level and protects the liver from further injury.

Lessions: A pregnant woman developed azithromycin-induced intrahepatic cholestasis. Physicians should be aware of this side effect of azithromycin, which is widely prescribed.

Abbreviations: ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, DILI = drug-induced liver injury, ICP = intrahepatic cholestasis of pregnancy, ULN = upper limit of normal.

Keywords: azithromycin, drug-induced liver injury, intrahepatic cholestasis of pregnancy, intrahepatic cholestasis

1. Introduction

Azithromycin belongs to a subgroup of macrolides, and it is a safe drug with less than a 5% incidence of clinical side effects.[1] Common side effects include headache, diarrhea, nausea, and dizziness. As an azalide antibiotic is derived from erythromycin, azithromycin can cause hepatotoxicity and has the potential to cause cross-reactivity.[2] Hepatotoxicity caused by prescription or nonprescription medications is commonly called drug-induced liver injury (DILI). It is difficult to assess the true incidence of DILI because of different diagnostic criteria and under-reporting. Thus far, only several cases of hepatotoxicity have been reported because of azithromycin in the English literature. Two patients had asymptomatic elevation of liver enzyme levels,[3,4] and another 4 patients had cholestatic hepatitis with jaundice after azithromycin administration.[5–9]

Intrahepatic cholestasis of pregnancy (ICP) is a unique hepatic disorder in pregnancy, and it has a recurrence rate of 40% to 70%. A diagnosis of ICP is made based on the presence of pruritus, elevated liver enzyme and serum bile acid levels, and the absence of disease that might produce similar laboratory values or symptoms, which resolve after delivery. However, most patients with ICP do not have elevated liver enzyme levels. ICP occurs during the late second or third trimester of pregnancy and disappears rapidly after delivery. The incidence is variable between 0.1% and 15.6% in different regions of the world.[10] The maternal prognosis of ICP is usually good, whereas ICP increases fetal morbidity and mortality, particularly with regard to preterm delivery, fetal distress, and sudden intrauterine fetal death.[11,12] Thus, it is important to establish clinical awareness of the potential adverse fetal outcome in ICP and consider it as a high-risk pregnancy disorder. The etiology of ICP is multifactorial, as it involves genetic, hormonal, and environmental factors.[10]

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Table 1

Laboratory test values of patient with azithromycin-induced-liver-injury.

Laboratory test (reference range)	Baseline value*	ER Vist	Hospital day		Clinic follow-up, days		Second Pre#	
			2	5	5	10	2 (w)	1 (w)
ALT (7–40U/L)	19	36.9	58.3	211.2	73	38	20.2	31
ALP (35–100U/L)	55	240	199.2	145.5	169	103	186.2	233.5
Total Bile Acid (0–12 μmol/L)	3.1	123.6	6.2	2.9	1.8	NR	5.1	8.6

ALP = alkaline phosphatase, ALT = alanine transaminase, NR = not reported.

* Baseline values obtained 2 weeks before emergency room (ER) vist; #In the second pregnancy, blood test values obtained 2 weeks and 1 week before baby birth

Here, we describe a pregnant woman who developed intrahepatic cholestasis closely related with azithromycin use, which has been rarely reported before.

2. Case report

A 30-year-old woman (79 kg, more than 38 weeks' pregnant) presented at our institution with generalized pruritus and an elevated serum bile acid level. She was in good health, except for symptoms of an upper respiratory infection. She took a 5-day course of azithromycin (500 mg loading dose and then 250 mg daily). On the fourth day of azithromycin treatment, she developed severe pruritus. Blood test results revealed an abnormal total bile acid level (more than 10-fold of the normal level), while the alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma-glutamyl transferase levels were normal. She denied taking other medications. She also denied alcohol use, herbal medication use, substance abuse, and other chemical exposure. She had no family history of liver disease. The ultrasonogram of the liver showed a good liver structure with no other positive symptoms. The laboratory tests are shown in Table 1. Before azithromycin administration, she showed no symptoms, and the liver enzyme and total bile acid levels were normal. After 4 days of treatment with azithromycin, she developed severe pruritus, and the serum total bile acid level increased significantly with normal hepatic aminotransferase levels. On the second day after cesarean section, hepatic aminotransferase levels increased slightly and reached its peak level on day 4 after cesarean section. The total bile acid level became normal after fetal delivery. The liver enzyme levels returned to normal within 4 weeks without any symptoms.

Management: (1) A diagnosis of ICP was made, and the patient was instructed to avoid using the antibiotic. (2) Cesarean section was performed immediately to lower the risk of fetal demise. The 1-minute, 5-minute, and 10-minute Apgar scores of the newborn baby were all 10. (3) The mother was re-evaluated when the liver enzyme level became elevated after cesarean section, and azithromycin-induced intrahepatic cholestasis was considered. Silymarin capsules and bifendate were prescribed to lower the liver enzyme levels and protect the liver from further injury.

Two years later, the same patient delivered her second baby without ICP recurrence or any hepatic injury (Table 1).

3. Discussion

ICP is the most common pregnancy-related liver disorder, and its pathogenesis is poorly understood. The ICP-associated gene is reported to be located in the p23 region of chromosome 2, similar to mutations in the hepatic phospholipid transporter (MDR3/ABCB4), aminophospholipid transporter (ATP8B1/FIC1), and bile salt export pump (BSEP/ABCB11). Estrogen is considered one of the multifactors causing cholestasis in experimental models and other clinical situations. A high level of estrogen in genetically predisposed individuals may induce intrahepatic cholestasis by impaired sulfation and the transport of bile acids,[13] but the detailed mechanisms need investigated more. Although environmental factors are considered as a cause based on seasonal and geographic variability, no specific etiologic factors have been clearly identified.

A diagnosis of ICP is made based on the presence of pruritus and an elevated bile acid level, which resolve after delivery, and the absence of diseases, which might manifest with similar laboratory values or symptoms. In this case, the diagnosis of ICP was made based on the patients' symptoms, high serum bile acid level, and the absence of diseases sharing the same symptoms and laboratory values. Interestingly, the total bile acid level reached a very high value (10-fold higher than the normal level) 3 days after azithromycin was administered (Table 1 and Fig. 1), whereas the liver aminotransferase levels increased more than 5 times the normal value on day 5 after cesarean section (Fig. 1). The patient took no antibiotics or drugs

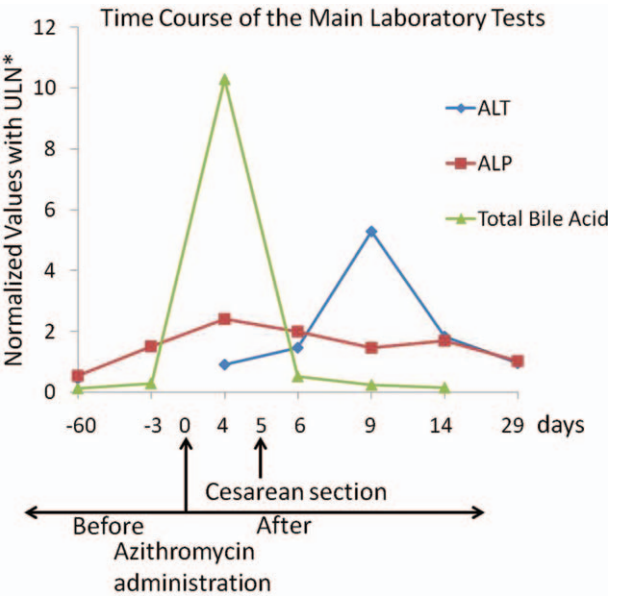

Figure 1. The laboratory values are increased following azithromycin administration. The first day of azithromycin prescription is marked as day 0. "Before" means that the laboratory values were obtained before azithromycin was taken. "After" refers to the laboratory values that were obtained after azithromycin was taken. On day 5 of azithromycin administration, cesarean section was performed for this patient. On day 4 of azithromycin administration, the total bile acid level reached a peak value and decreased within normal range after the baby was delivered. The ALT level increased to 5.28 times the ULN on day 9 of azithromycin administration. The ALP level was high all the time, which might have been caused by the fetus. ALP = alkaline phosphatase, ALT = alanine transaminase, ULN = upper limit of normal. The "−60" means that the laboratory test was obtained 60 days before azithromycin.

other than oxytocin, which is proven safe in woman during delivery. The increased liver aminotransferase levels indicate that liver dysfunction is probably caused by azithromycin.

Azithromycin is primarily metabolized by the liver and generally well tolerated, with less than 1% of patients developing adverse effects.[2] Most adverse effects are relatively mild, such as nausea, diarrhea, abdominal pain, and vomiting. Nevertheless, several reports of hepatotoxicity secondary to azithromycin have been published in the literature. The reason why azithromycin induces liver injury may be because azithromycin is an azalide antibiotic derived from erythromycin, both of which can produce hepatotoxicity and have the potential to cause cross-reactivity.[2] Previous studies about hepatotoxicity due to azithromycin use reported DILI as the diagnosis. We were very careful about making a diagnosis of DILI in our patient since there are no diagnostic tests or biomarkers for DILI.[14] In current guidelines established by the Council for International Organizations of Medical Sciences (CIOMS), alkaline phosphatase (ALP) and ALT levels are the principle clinical indexes for diagnosing and classifying DILI. Based on the classification by CIOMS, there are 3 types of DILI: hepatocellular, cholestatic, or mixed DILI. Cholestatic DILI is characterized by an ALP level $\geq$2 upper limit of normal (ULN) and R $\leq$2 (R = (ALT/ALT ULN)/(ALP/ALP ULN)); and hepatocellular and cholestatic mixed DILI is characterized by an ALT level $\geq$3 times ULN, ALP $\geq$2 times ULN, and $2 < R < 5$. In the present case, in the early stage, the ALP level was 240 U/L (reference range: 35–100 U/L) and R was 0.38, which met the diagnostic standard of cholestasis DILI. However, the ALT level increased to 211.2 U/L (reference range: 7–40 U/L), ALP level was 145.5U/L (reference range: 35–100 U/L), and R was 3.63, indicating hepatocellular and cholestatic mixed DILI. The Roussel Uclaf Causality Assessment Method (RUCAM) is a well-established tool in common use to quantitatively assess causality in cases of suspected DILI, and RUCAM is used to assess causality for DILI. The RUCAM score of this case was 7, which indicates a probable relationship of azithromycin and liver injury. Thus, the liver injury in this case was probably caused by azithromycin. Considering that ICP is a diagnosis of exclusion, it is more reasonable to make a diagnosis of azithromycin-induced ICP.

This is the first report about azithromycin-induced intrahepatic cholestasis in a pregnant woman since azithromycin-induced intrahepatic cholestasis is rarely reported in adult individuals, let alone in pregnant women. In this case, the pruritus, elevated bile acid level, normal liver enzyme level, and few clinical side effects reported of azithromycin at the beginning of the patient's clinical course made it difficult to distinguish between ICP and azithromycin-induced intrahepatic cholestasis. Azithromycin-induced intrahepatic cholestasis was diagnosed when all the factors were re-evaluated, such as the ALT level and use of azithromycin. In summary, we concluded that the pregnant woman developed intrahepatic cholestasis induced by azithromycin.

The management of DILI includes early recognition and withdrawal of the offending drug. The recognition of macrolide-induced liver injury is important because discontinuation of the drug usually results in complete recovery. Rarely, macrolides-induced liver injury might progress to chronic liver diseases, such as ductopenia and vanishing biliary duct syndrome. Different from the previously published cases, our patient developed symptoms similar to ICP, which might threaten the fetus's life. Thus, cesarean section was performed. Our patient fully recovered with the resolution of symptoms and the liver function test values returned to baseline within 1 month after exposure to azithromycin with treatment of silymarin capsules and bifendate, which were prescribed to lower the liver enzyme levels and protect the liver from further injury.

Physicians should be aware of this side effect of azithromycin and be cautious when prescribing azithromycin to pregnant women in the future.

4. Teaching points

What makes this case unique is that azithromycin-induced intrahepatic cholestasis in pregnant women is characterized by the same symptoms as ICP in the early stage followed by elevated liver enzyme levels. Most reported cases of hepatotoxicity induced by azithromycin are well controlled by drug withdrawal. In this case, the same symptoms as ICP developed before severe liver injury, but there is no guideline or data of how to control drug-induced intrahepatic cholestasis in pregnant women. ICP is life threatening for the fetus, but the exact pathophysiology that leads to fetal demise is unknown. Whether drug-induced ICP may threaten the fetus's life needs more investigation. However, first, management of azithromycin-induced intrahepatic cholestasis is the most important thing to protect the pregnant woman and fetus since it shares the same clinical manifestation as ICP. Thus, being aware of this side effect of azithromycin, physicians should be cautious to prescribe azithromycin to pregnant women.

5. Supplementary index for Figure 1

Procedure for obtaining the laboratory test results: The pregnant woman underwent a blood test every 2 months. Three days before azithromycin administration, she underwent a routine blood test, and 7 days later, she developed severe pruritus. The physician performed 1 more blood test. After cesarean section (6), another blood test was performed to evaluate the bile acid level, and the result shows mild elevation of ALT and AST levels. On the day the patient returned home (9), the physician tested her blood to check whether the ALT and AST levels were normal. As shown, the ALT level is 5 times the upper limit of normal, which was very high. Then the patient was prescribed silymarin capsules and bifendate to lower the liver enzyme levels, and another 2 blood tests were performed until the liver enzyme levels recovered.

6. Ethical review

This study was performed according to the protocols approved by the Ethical Committee of Qianfoshan Hospital. We obtained informed consent from the patient to publish this case and accompanying images.

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