CASE REPORT

Possible Atazanavir-Induced Cholelithiasis in a Pregnant Woman: A Case Report

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INTRODUCTION

For treatment-naive adult patients infected with HIV, the first-line antiretroviral regimen consists of 2 nucleoside reverse transcriptase inhibitors in combination with an integrase inhibitor or a boosted darunavir regimen.[1] As of April 2015, the US Department of Health and Human Services replaced atazanavir with an alternative protease inhibitor regimen in its guidelines for adults and adolescents.[1] However, the most recent update (in August 2015) of the same organization's perinatal guidelines confirmed that during pregnancy, ritonavir-boosted atazanavir is still considered a first-line protease inhibitor option, because there has been extensive experience in this clinical setting with no adverse infant outcomes.[2] Atazanavir has been associated, in both adult and pediatric populations, with unconjugated hyperbilirubinemia, a phenomenon that usually occurs without clinical complications.[3] In one retrospective study involving 155 pregnant women who were exposed to atazanavir, the drug was reported to be generally well tolerated, with 63.2% of the patients reporting no side effects.[4] Nausea was the most commonly observed adverse event (in 34.2% of patients), and about 2% of the women stopped treatment because of side effects.[4] Cholelithiasis was not reported in phase III clinical trials of ritonavir-boosted atazanavir.[3] However, recent postmarketing reports have suggested a potential association between this regimen and cholelithiasis. Here, we describe a case of cholelithiasis in a pregnant woman who was taking ritonavir-boosted atazanavir. To our knowledge, this is the first reported case of this form of toxicity during pregnancy.

CASE REPORT

A 35-year-old HIV-positive Haitian woman was admitted to an obstetrics and gynecology emergency unit on the night of March 31, 2014, at 35 weeks' gestational age, with hyperemesis gravidarum and severe epigastric pain.* It was her fourth pregnancy. The physical examination revealed right upper quadrant abdominal tenderness and scleral icterus. The patient was unable to communicate the level of pain clearly, despite questioning. As noted in the medical chart, her body mass index (BMI) had been normal before the pregnancy, at about 22 kg/m^2, and at 30 weeks' gestational age, the BMI remained normal, at 23.6 kg/m^2. A complete work-up was performed, including measurement of liver and pancreatic enzymes, complete blood count, abdominal ultrasonography, and renal function tests. Alkaline phosphatase and total bilirubin values were mildly elevated (112 U/L [normal range 22–87 U/L] and 62 µmol/L [normal range 5–21 µmol/L], respectively) (Figure 1), and other liver enzyme values were normal (alanine aminotransferase 16 U/L [normal range 5–34 U/L], aspartate aminotransferase 21 U/L [normal range 11–43 U/L], γ-glutamyltransferase 24 U/L [normal range 7–65 U/L]). Hypoalbuminemia (albumin 27 g/L [normal range 38–48]) and hyperamylasemia (amylase 139 U/L [normal range 20–108 U/L]) were also observed. No lipase or glucose values were obtained during the hospital stay. Hematologic parameters revealed normocytic, normochromic anemia (hemoglobin 93 g/L [normally > 110 g/L]), mean corpuscular volume 100.0 fL (normal range 80–100 fL), mean corpuscular hemoglobin content 33.7 pg (normal range 26–34), and thrombocytopenia (platelet count 112 × 10^9/L [normal range 140–440 × 10^9/L]). Renal function was normal (calculated creatinine clearance > 90 mL/min), and the results of serologic tests for viral hepatitis infection (hepatitis A, B, and C) were negative.

The patient's regular medications included folic acid 5 mg once daily, ferrous sulphate 300 mg twice daily, and

*Patient consent could not be obtained for publication of this case report, despite attempts to reach the patient after discharge for follow-up care. Potentially identifying details not pertinent to understanding the case have been removed from the manuscript.

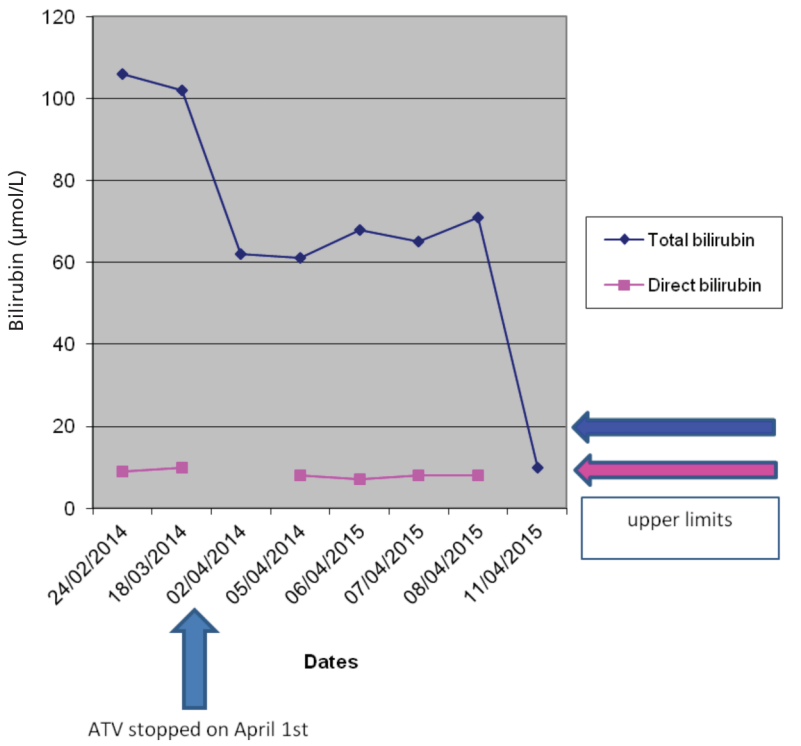

Figure 1. Bilirubin levels in a pregnant woman infected with HIV. Dates are presented as day/month/year. The bilirubin values for dates in February and March 2014 were obtained during routine monitoring; the presentation described in the case report occurred in April 2014. The horizontal scale is not proportional. The upper limits of normal for total and direct bilirubin are indicated by arrows at bottom right of the graph. ATV = atazanavir.

ciprofloxacin 0.3% ophthalmic drops. The hospital pharmacist contacted the community pharmacist to verify the list of current medications, at which time the medical team was informed that the patient had been on antiretroviral therapy for the past 16 years. During her previous pregnancies, she had been receiving triple therapy consisting of abacavir 300 mg, lamivudine 150 mg, and zidovudine 300 mg twice daily with no problems. According to medical records, in 2005, during her second pregnancy, there had been suspicion of pancreatitis because of retrosternal pain and elevated amylase (101 U/L), without digestive symptoms. No lipase or bilirubin values or imaging were available from this previous hospitalization.

Since 2006, the patient had been taking atazanavir 200 mg twice daily boosted with ritonavir 100 mg daily, as well as the combination agent abacavir–lamivudine 600/300 mg daily. HIV RNA had been undetectable since 2007. As part of regular monitoring for antiretroviral toxicity, in February 2014, total bilirubin was already elevated (112 U/L) without any significant clinical symptoms (Figure 1). In March 2014, the CD4 lymphocyte count was 462 cells/µL. On April 1, 2014, the day after admission, the CD4 lymphocyte count was 476 cells/µL and HIV RNA was less than 40 copies/mL (undetectable).

Because of the presence of biliary sludge and microlithiasis, seen on abdominal ultrasonography, and in view of the patient's continuing severe epigastric pain and vomiting, the antiretrovirals were discontinued on the second day of the hospital stay. There was no attempt to extract gallstones by endoscopic retrograde cholangiopancreatography, because of the pregnancy. Six days after discontinuation of the antiretrovirals, the patient reported improvement in her abdominal pain, and the need for analgesics (hydromorphone) subsided; there was also subsequent normalization of total bilirubin (10 µmol/L) (Figure 1) and little change in the other laboratory values (alanine aminotransferase 19 U/L, aspartate aminotransferase 23 U/L, amylase 179 U/L [i.e., remained elevated], hemoglobin 107 g/L, and platelets 114 × 10^9/L). Antiretroviral therapy was restarted, with raltegravir 400 mg twice daily and emtricitabine–tenofovir 300/200 mg once daily. The differential diagnosis included pancreatitis, hepatitis, preeclampsia, and drug-related hepatotoxicity. After exclusion of these diagnoses, the emesis and abdominal pain were attributed to potential cholelithiasis,

possibly caused by the atazanavir-containing antiretroviral regimen.

The patient delivered a healthy 3-kg baby at gestational age 37 weeks and 5 days (18 days after admission). Three weeks after the delivery, bloodwork was repeated at the time of a minor procedure; platelets (215×10^9/L) and hemoglobin (130 g/L) were increased, but such increases are usually observed in the postpartum period. Despite subsequent attempts to contact the patient, we were unable to reach her to follow up on her condition and obtain additional laboratory values.

DISCUSSION

To the authors' knowledge, this is the first report of an acute episode of cholelithiasis in an HIV-positive multiparous pregnant woman who was receiving treatment with an atazanavir-containing regimen. According to the Naranjo probability scale, the likelihood of atazanavir-induced cholelithiasis in this case was "possible" (total score of 3, based on previous reports of such an association [+1], appearance of the problem after drug administration [+2], improvement with discontinuation [+1], and the possibility of alternative causes, such as pregnancy [–1]).[5] Barbara and others[6] showed a link between the number of pregnancies and the prevalence of gallstones. In fact, the prevalence of cholelithiasis was significantly higher among multiparous women than among nulliparous or primiparous women. Other risk factors for cholelithiasis include obesity, hyperbilirubinemia, and *UGT1A1* polymorphism, as well as a history of cholelithiasis. Hyperbilirubinemia in HIV-infected adults treated with atazanavir is due to competitive inhibition of the bilirubin-conjugating enzyme uridine diphosphate glucuronyltransferase 1A1.[7] In a study of 106 patients infected with HIV and treated with ritonavir-boosted atazanavir, Lankisch and others[7] reported that 15% of patients had normal bilirubin levels (< 19 µmol/L), 11% had grade 1 hyperbilirubinemia (19–26 µmol/L), 37% had grade 2 hyperbilirubinemia (26–43 µmol/L), 31% had grade 3 hyperbilirubinemia (43–85 µmol/L), and 6% had grade 4 hyperbilirubinemia (> 85 µmol/L). Demographic and genetic factors also seem to play a role, with gallstone formation being most prevalent among North American First Nations, native Chileans, and Hispanics, as well as northern Europeans and nonindigenous North Americans, and is less commonly reported among Asians and African Americans.[8] The patient described here was multiparous and had hyperbilirubinemia; however, she was not obese and was of Haitian descent.

Outside the context of pregnancy, other authors have reported cases of cholelithiasis associated with drugs, in particular, antiretrovirals and protease inhibitors. The association between indinavir and cholelithiasis was initially described by Verdon and others.[9] Analysis by infrared spectrophotometry showed that 50% of the gallstones consisted of the antiretroviral drug.[9] Jacques and others[10] reported choledocholithiasis associated with an atazanavir-containing regimen in a 47-year-old HIV-infected African woman. In another case, a gallstone was identified in an HIV-infected man 1 year after therapy was switched from ritonavir-boosted atazanavir to a darunavir–ritonavir and tenofovir–emtricitabine regimen; the concentration of atazanavir in the gallstone was significant (6.0 mg/g).[11] Fourteen additional cases of HIV-infected patients (12 men and 2 women) who were receiving an atazanavir-based antiretroviral regimen and who developed complicated cholelithiasis have been reported.[12] Symptoms appeared after a median duration of 42 months (range 1–90 months), which suggests that prolonged exposure to atazanavir may be a possible risk factor for cholelithiasis. Calculi from 11 of the patients were sent for infrared spectrometry analysis; for 8 of these 11 cases, the median atazanavir proportion, relative to total calculus composition, was 89%.[12] Another study showed an association between the incidence of cholestasis, including asymptomatic cholelithiasis, and prolonged exposure to ritonavir-boosted atazanavir.[13] Patients treated with this regimen for more than 2 years were twice as likely to develop gallstones as patients treated for less than 2 years. Moreover, Barbara and others[6] found that 20% of patients with cholelithiasis experienced symptoms over the long term. Like our patient, these latter cases occurred after long-term treatment (56 months) and presented with abdominal pain.[6] Hamada and others[14] compared the incidence of complicated cholelithiasis in patients receiving ritonavir-boosted atazanavir and patients receiving other protease inhibitors (unboosted fosamprenavir, ritonavir-boosted fosamprenavir, lopinavir–ritonavir, or ritonavir-boosted darunavir), and found no statistically significant difference between the 2 groups. However, the median observation period in that study[14] (31.7 months) was shorter than the 8-year treatment period for the patient described in the current report; our patient's longer treatment period could have contributed to the gallstone formation.

In a report published in 1997, Erlinger[8] showed that gallstones can be induced by several drugs. Two mechanisms were hypothesized for atazanavir-induced cholelithiasis.[8] The first was precipitation of the drug itself in the bile, leading to development of a gallstone consisting of the drug and some other biliary components (mainly calcium). The solubility of atazanavir is optimal at lower pH values, whereas biliary pH is usually above 6.5, which could lead to crystallization and subsequent cholelithiasis.[3] The second proposed mechanism was an atazanavir-induced increase in production of one of the components of gallstones (such as bilirubin or cholesterol). In the case described here, cholesterol was not measured during the patient's pregnancy, because pregnancy can affect cholesterol levels. The patient presented with elevated total bilirubin without a significant increase in alanine aminotrans-

ferase, aspartate aminotransferase, or γ-glutamyltransferase; these results indicate that atazanavir did not lead to hepatic toxicity. Both of the mechanisms proposed by Erlinger[8] may have contributed to the development of cholelithiasis in the patient described here.

This case report was limited by a lack of information about the patient. In particular, her family history, social history, and clinical follow-up were missing, but such information would be needed to achieve a complete review of the case. Furthermore, the composition of the gallstones was not analyzed, so other causes of the cholelithiasis cannot be ruled out. However, the patient's symptoms improved substantially upon discontinuation of atazanavir. The mechanisms by which atazanavir-containing gallstones are formed remain to be elucidated.

CONCLUSION

The occurrence of cholelithiasis in this HIV-infected pregnant multiparous woman could have been associated with her regimen of ritonavir-boosted atazanavir, given that the symptoms resolved upon discontinuation of the drug. This case raises awareness of a possible association between atazanavir and cholelithiasis, which should be considered as part of the differential diagnosis in pregnant women who present with nausea, vomiting, and abdominal pain.

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