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Severe prolonged cholestatic hepatitis caused by exemestane

Ting Bao,

The University of Maryland Marlene and Stewart Greenebaum, Cancer Center, S9D, 22 S. Greene Street, Baltimore, MD 21201, USA, tbao@umm.edu

John Fetting,

The Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University School of Medicine, Baltimore, MD, USA

Laura Mumford,

The Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University School of Medicine, Baltimore, MD, USA

Jane Zorzi,

The Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University School of Medicine, Baltimore, MD, USA

Karineh Shahverdi,

The Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University School of Medicine, Baltimore, MD, USA

Stacie Jeter,

The Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University School of Medicine, Baltimore, MD, USA

Frank Herlong,

The Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University School of Medicine, Baltimore, MD, USA

Vered Stearns, and

The Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University School of Medicine, Baltimore, MD, USA

Linda Lee

The Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University School of Medicine, Baltimore, MD, USA

Aromatase inhibitors (AIs) are used as first-line adjuvant hormonal therapy in postmenopausal women with hormone receptor-positive breast cancer, either as monotherapy or sequential therapy after tamoxifen [1–6]. Unlike tamoxifen, the former gold standard adjuvant hormonal therapy, AIs cause musculoskeletal symptoms, osteoporosis, and bone fractures [1–6]. Although AIs such as letrozole and anastrozole also cause liver enzyme elevation unrelated to liver metastasis in 3–5% patients,^{1,2} severe hepatotoxicity has rarely been associated with AIs. We report a case of severe prolonged cholestatic hepatitis caused by exemestane.

Case report

A 47-year-old postmenopausal white, non-Hispanic woman with no significant past medical history was diagnosed with stage I (T1a, N0, M0) breast cancer. The tumor was a 4 mm, ER positive, PR weakly positive, HER2 negative, Ki67 1%, grade I infiltrating ductal carcinoma for which she underwent lumpectomy with sentinel lymph node biopsy. She had no known drug allergies and was taking only naproxen 550 mg orally, about thrice a week due to sports-related wrist discomfort. She consumed no alcohol and did not use any nutritional or dietary supplements. Given a strong family history of breast cancer and confirmed postmenopausal status, the patient was enrolled in a clinical trial in which women were randomized to the AI exemestane or letrozole to assess pharmacogenetics end-points. She was randomized to and initiated exemestane 25 mg daily. Her baseline laboratory parameters, including cell counts and chemistry panel, were all within normal limits.

Three weeks after initiating exemestane, the patient reported fatigue, jaundice, and pruritis, associated with elevated total bilirubin, aspartate amino transferase (AST), alanine amino transferase (ALT), and alkaline phosphatase (ALP) (Table 1). Hepatitis serologic tests, including hepatitis A IgM, hepatitis B surface antigen, hepatitis B core IgM, and hepatitis C antibody, were negative. Autoantibodies associated with autoimmune hepatitis, including antimitochondrial antibody (AMA) and antinuclear antibody (ANA), were also negative. Exemestane was discontinued.

Three weeks following exemestane discontinuation, the serum total bilirubin was 16.2 mg/dl with stabilization of other hepatic enzymes (Table 1). Right upper quadrant ultrasonography showed no fixed defect of the bile duct. The patient was started on ursodiol, but her total bilirubin continued to increase to maximum level of 21.2 mg/dl (Table 1). She was subsequently hospitalized for 11 days for debilitating pruritus as a result of persistently severe cholestasis, causing excoriated skin, dehydration, anxiety, and depression. While in the hospital, she was treated with cholestyramine, phenobarbital, lorazepam for symptom control, and with venlafaxine for depression. Four months after discontinuation of exemestane, the patient's total bilirubin fell to 1.5 mg/dl (Table 1). Her liver enzymes, AST, ALT, and ALP, remained elevated until after venlafaxine was discontinued (Table 1).

Discussion

Our patient's clinical presentation and the temporal correlation of drug exposure and onset of symptoms suggest exemestane-induced prolonged cholestatic hepatitis. Exemestane is a third-generation steroidal AI and has been widely used as adjuvant endocrine therapy for postmenopausal women with hormone receptor-positive breast cancer. In the inter-group exemestane study (IES), 92.5% of the 2,146 patients taking exemestane had some adverse results; however, hepatotoxicity was not reported [2, 7]. Exemestane-induced hepatic toxicity was only reported in one case report published in Spain in 2003 in a 65-year-old woman with metastatic breast cancer to bone only, who developed severe cholestatic hepatitis 2 months after she began exemestane [8]. Her total bilirubin rose to 13.83 mg/dl with a direct fraction of 11.25 mg/dl, AST 45 U/l, ALT 69 U/l, and ALP 690 U/l. She recovered quickly after exemestane discontinuation, and her laboratory parameters normalized about 4 months later.

Another 89-year-old woman developed cholestatic hepatitis 2 months after initiating anastrozole in Spain [9]. She had a total bilirubin of 3.55 mg/dl, direct bilirubin 1.63 mg/dl, AST 255 U/l, ALT 410 U/l, and ALP 231 U/l. Three days after drug withdrawal, her hepatic enzyme and bilirubin improved significantly with a total bilirubin of 0.79 mg/dl, AST 23 U/l, ALT 100 U/l, and ALP 133 U/l. They all subsequently normalized about 2 weeks later [9].

In another case in Spain, a 58-year-old woman developed severe cholestatic hepatitis 3 weeks after taking anastrozole. She also had thrombocytopenia, prolonged prothrombin time, significantly elevated liver enzymes with AST, ALT and ALP in the thousands, and total bilirubin 187 $\mu\text{mol/l}$ which is equal to 11 mg/dl. Her liver enzymes improved significantly 1 month after anastrozole discontinuation, but the patient then developed pneumoperitoneum from a perforated duodenal ulcer and died from septic shock [10].

Drug-induced hepatotoxicity is usually present 5–90 days after the initial drug exposure [11]. Some patients with cholestatic hepatitis have fever, anorexia, right upper quadrant abdominal discomfort, nausea, jaundice, and pruritus. Hepatic enzyme showed a cholestatic pattern. Although most drug-induced liver injuries are reversible, on rare occasions, the toxicity may be irreversible and may lead to liver failure, permanent damage to small bile ducts in “vanishing bile duct syndrome,” secondary biliary cirrhosis, or sclerosing cholangitis [11]. A recent prospective study of 300 patients reported that prescription drugs accounted for 73% of drug-induced liver injury in U.S., whereas vitamins and herbal supplements accounted for only 9%. Antibiotics were the most common cause of drug-induced hepatotoxicity with amoxicillin–clavulanate being the most frequently cited causative agent. AIs, especially exemestane, however, were not listed as one of the causative agents [12].

Multiple mechanisms have been suggested to explain drug-induced hepatotoxicity [11]. Drugs may disrupt intracellular calcium homeostasis, resulting in rupture of actin fibrils forming the cell membrane and cause cell lysis [13]. Drugs may also interact with transport protein in the canaliculus and interrupt bile flow, causing predominantly cholestasis [13]. Genetic defects in bile transporters may also promote cholestasis. [11] In addition, drugs may form covalent bonds to certain enzymes forming adducts, which may then activate immune response causing an immune mediated reaction, resulting in apoptosis [14].

Exemestane, a steroidal AI, forms irreversible covalent bonds to, and completely inactivates, the aromatase enzyme. Exemestane is metabolized in the liver and forms a number of metabolites, with little knowledge of their toxic potential. A series of events may have occurred to explain our patient’s exemestane-induced severe cholestatic hepatitis. She may have a genetic predisposition with sensitivity to an exemestane-aromatase adduct that resulted in a severe immune response. For example, a specific HLA haplotype was found in 57% of patients who developed amoxicillin–clavulanate-induced hepatitis, whereas it was only found in 12% of patients who did not have adverse reaction [15]. She may have a pharmacogenetic polymorphism that generates toxic liver metabolites from exemestane or prevents effective excretion of an exemestane metabolite. Drug–drug interaction may have contributed to explain her severe reaction. Nonsteroidal anti-inflammatory drugs have been associated with drug-induced cholestatic hepatitis. Our patient had been taking low dose naproxen thrice a week for approximately 3 years; therefore, the chance of naproxen-induced hepatotoxicity is less. However, it is possible that there was an idiosyncratic interaction between exemestane and naproxen through cytochrome-mediated drug–drug interaction altering exemestane plasma concentration and causing liver injury.

So far, three cases of AI-induced hepatotoxicity have been reported, and all the three of them occurred in Spain. Our case is the first reporting of AI-induced hepatotoxicity that occurred in a non-Hispanic woman in the U.S. In addition, our case is the only one that reported severe cholestatic hepatitis as a result of AI. After we reported our case to the company that manufactures exemestane, Pfizer, they added “cases of hepatitis including cholestatic hepatitis have been observed in clinical trials and reported through post-marketing surveillance” to the package insert.³

AI is a relatively new class of drug and has become standard first-line hormonal therapy for postmenopausal women with hormone receptor-positive breast cancer [6]. In the past 10 years, thousands of women have been taking AIs without significant adverse reactions. AI-induced hepatotoxicity is one of the most severe adverse reactions reported so far. Our case illustrates the importance of an awareness of AI-induced hepatotoxicity with discontinuation of the drug. Overall, we believe that the benefits of adjuvant AI therapy outweigh the potential risk. However, AI-induced hepatotoxicity should be considered when the patient with breast cancer developed abnormal liver enzymes when treated with AI.

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³Pfizer, Aromasin (exemestane tablets) package insert, 2007.

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Table 1

Liver enzymes changes

Variable	Reference range	Baseline	3 weeks after exemestane initiation	Weeks after exemestane discontinuation				
				3	4	8	16	24
Total bilirubin (mg/dl)	0.2–1.5	0.8	3.8	16.2	21.2	19.7	1.5	0.5
AST (U/l)	0–35	30	170	41	44	59	163	58
ALT (U/l)	4–40	38	438	73	54	74	186	83
ALP (U/l)	30–115	56	181	188	184	197	546	266