Transient Hepatitis Secondary to Zoledronic Acid in a Woman with Sheehan Syndrome

Sir,

Patients with Sheehan syndrome (SS) have low bone mineral density mainly because of gonadotroph and somatotroph deficiency together with long-term thyroxine and glucocorticoid treatment.[1,2] Bisphosphonates along with calcium and vitamin D supplementation are commonly used for the treatment of osteoporosis. Zoledronic acid (ZA) prescribed as yearly infusion is safe and well tolerated except transient and self-limiting flu-like symptoms. Here, we report a patient of SS who developed mild transient hepatitis after ZA infusion.

A 55-year-old woman was diagnosed with SS 6 years back based on post-partum haemorrhage, lactotroph, gonadotroph, thyrotroph and corticotroph failure and empty sella on MR imaging. She was prescribed thyroxine (75 micrograms daily) and prednisolone (5 milligrams daily) along with elemental calcium of 500 mgs and 1000 units of cholecalciferol daily. DXA scan revealed osteoporosis (T-score L1-L4 spine = -3.9). She is a non-smoker, does not consume alcohol and did not take any other drug causing liver disease. Her baseline liver function test (LFT) was within normal limits [Table 1]. The patient received injection ZA, 5 mgs in 100 ml of ready-to-infuse solution (Stoplos One 5 mgs/100 ml; Akums Drugs and Pharmaceuticals Ltd., Haridwar, India) over a period of 30 minutes. Few hours after the infusion, she experienced flu-like symptoms; these symptoms continued on the second day. On the second day, clinical examination revealed an icteric tinge. LFT revealed hyperbilirubinemia with elevated liver enzymes, aspartate aminotransferase (AST), alanine aminotransferase (ALT) and gamma-glutamyl transpeptidase (GGT) [Table 1]. Ultrasound revealed evidence of grade 1 fatty liver without any focal lesion of liver parenchyma and biliary tract. A diagnosis of acute hepatitis was considered, and she was further investigated for the aetiology of hepatitis. Serological tests for hepatitis A, B, E and C were negative, ruling out the possibility of viral hepatitis. Meanwhile, C-reactive protein (CRP), antinuclear antibody–indirect fluorescent antibody (ANA-IFA), anti-mitochondrial antibody (AMA) and anti-smooth muscle antibody were negative, ruling out the possibility of autoimmune hepatitis [Table 1]. In view of a normal LFT before ZA infusion, clinical jaundice, abnormal liver enzymes, negative viral and autoimmune screen, possibility of drug-induced liver injury secondary to ZA was entertained. The patient was managed conservatively and was kept in hospital for observation. The patient had a normal appetite and did not need parental fluids. LFTs were repeated at days 3, 5 and 6, which revealed a downward trend and finally normalization of liver enzymes on day 6.

As many as one-third of ZA-naïve patients experience an acute phase reaction manifesting as fever, myalgia, headache or other flu-like symptoms. The other rare potential side effects of ZA are atrial fibrillation, uveitis, osteonecrosis of the jaw (ONJ) and atypical femoral fracture.[3] Few cases of drug-induced liver injury because of ZA are reported. The liver injury may be mild and transient or severe and recurrent requiring glucocorticoids.[4-6] Our patient had a mild and transient liver injury, which resolved within a week. Idiosyncratic sensitivity to ZA may be the cause of liver injury in the present patient. The clinical significance of mild and transient liver injury may be mild, but clinicians should be aware of this adverse effect, and it may be advisable to get a routine LFT performed before administering a dose of ZA.

Table 1: Serial liver function tests in the patient with zoledronic acid-induced hepatitis

Parameter	Normal value	Pre-treatment	Day 1	Day 3	Day 5	Day 6
Bilirubin	0.30-1.50 (mg/dl)	1.6	3.5	3.8	1.58	1.36
AST	0-40 (U/L)	30	120	-	-	31
ALT	0-45 (U/L)	22	126	131	78	53
ALP	30-141 (U/L)	-	104	86	99	81
GGT	2-55 (U/L)	-	195	-	-	169
Albumin	3.50-5.20 (g/dl)	4.79	4.95	4.65	4.40	4.56
WBC	4-11 (/µL)	4900	6900	6700	8200	-
CRP	<6 (mg/L)	-	-	<6	-	-
ANA-IFA	(1:80 dilution)	-	-	Negative	-	-
AMA	< 20 (IU/mL)	-	-	11.14	-	-
ASMA	<20 (IU/mL)	-		12.69	-	-

AST=aspartate aminotransferase, ALT=alanine aminotransferase, ALP=alkaline phosphatase, GGT=gamma-glutamyl transpeptidase, WBC=white blood cell count, CRP=C-reactive protein, ANA-IFA=antinuclear antibody–indirect fluorescent antibody, AMA=anti-mitochondrial antibody, ASMA=anti-smooth muscle antibody

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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