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Letter to the Editor

Tamoxifen and fulvestrant induced steatohepatitis with cirrhosis: A rare case report

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Dear Editor,

Tamoxifen has improved the survival of patients with breast cancer. One of the less-recognized side effects is hepatic steatosis in 30%–40% of patients diagnosed on radiology, which progresses in 1%–2% to steatohepatitis and rarely to cirrhosis. Fulvestrant-induced acute hepatotoxicity has rarely been reported in literature.[1] Tamoxifen has also rarely been associated with cirrhosis and submassive hepatic necrosis.[2,3]

A 58-year-old postmenopausal female with well-controlled diabetes, hypertension, hypothyroidism, and body mass index of 26 kg/m^2 was diagnosed with right locally advanced breast cancer in August 2007. The histopathology showed the presence of invasive ductal carcinoma, Grade III, and it was strongly positive for the estrogen and progesterone receptors. She underwent modified radical mastectomy and subsequently was treated with adjuvant chemotherapy with doxorubicin, cyclophosphamide, and paclitaxel sequentially followed

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by radiotherapy. She was started adjuvant tamoxifen 20 mg once daily. Three years later in August 2010, she presented with hepatomegaly and deranged liver function tests (LFTs) with aspartate transaminase and alanine transaminase were 114 and 67 U/L, respectively and radiology suspicious of liver metastasis [Figure 1]. Tamoxifen was thus stopped. The patient, however, defaulted at this time. When she returned 6 months later, her hepatomegaly had reduced and liver function improved. Thus, tamoxifen-induced liver injury was suspected and proven on liver biopsy, which revealed portal fibrosis with portoportal bridging fibrosis and ballooning degeneration with steatohepatitis [Figure 2]. She was then started on letrozole. Her LFT remained normal. She had a locoregional recurrence after 4 years in June 2014, for which she underwent wide local excision and palliative radiotherapy and letrozole was changed to exemestane with no deterioration in LFT. In September 2017, she again had a second locoregional recurrence and exemestane was changed to fulvestrant. Within 4 months, however, she had worsening of LFT. Subsequent imaging did not reveal any metastasis. Fulvestrant was stopped because of suspected drug-induced liver injury and letrozole was restarted. Her LFT, however, progressively deteriorated and

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she developed cirrhosis with ascites and portal hypertension with small esophageal varies. Other causes of cirrhosis (autoimmune profile, viral serology, and nonalcoholic fatty liver diseases) were excluded. Thus, the patient had progressive liver dysfunction, leading to significant morbidity.

This is an unusual case where the patient had tamoxifen-induced steatohepatitis, which resolved after stopping tamoxifen and recurred after starting fulvestrant several years later, subsequently progressing to cirrhosis and liver failure.

Tamoxifen causes increased *de novo* fatty acid synthesis and inhibition of mitochondrial fatty acid β-oxidation in the liver, subsequently leading to macrovacuolar steatosis. This risk increased with concomitant obesity, type II diabetes, and metabolic syndrome. Fulvestrant's hepatotoxicity is possibly caused by its immunogenic metabolite. In postmenopausal women, aromatase inhibitors displayed less fatty liver disease compared to tamoxifen or fulvestrant, suggesting a more favorable hepatic safety profile.

In conclusion, this is a rare case of steatohepatitis and later cirrhosis induced by antiestrogenic therapy. As this can at times masquerade as metastasis, it may be important to biopsy doubtful cases, especially if liver functions improve after stopping the drug. Thus, physicians should be alert to the possibility of drug-induced liver injury with both tamoxifen and fulvestrant.

Declaration of patient consent

The authors certify that they have obtained all appropriate

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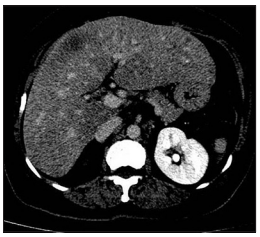

Figure 1: Contrast-enhanced computed tomography scan showed a hypodense lesion of the liver suggestive of metastatic

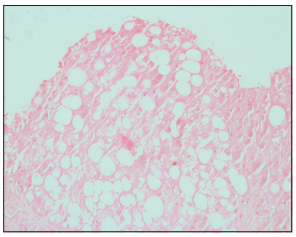

Figure 2: Histopathology from liver biopsy showed portal fibrosis with portoportal bridging fibrosis with ballooning degeneration

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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