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Case Report

Tamoxifen-associated liver hematoma in early-stage breast cancer: a case report

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ABSTRACT

A 44-year-old African American female with a previous medical history of major depressive disorder presented to the hospital with a dense feeling on her right breast following self-examination. Pathology report after right breast lumpectomy revealed the diagnosis of invasive ductal carcinoma (ER+, PR+ and HER2-) of the right breast. Nine months after the diagnosis, a combination of local radiotherapy with chemotherapy with tamoxifen (20 mg tablet/day) was started. Two months post tamoxifen initiation, the patient presented at the hospital with right upper quadrant abdominal pain with sharp and stabbing characteristics, radiating to the right shoulder. Abdominal/pelvic CT with contrast revealed that the patient developed a 25×58×85 mm subcapsular hematoma of the right anterior lobe of the liver. Our case suggests the development of liver hematoma with thrombocytopenia associated with tamoxifen therapy. Following tamoxifen administration, there was a significant drop in the platelet count from 139×10^9 /L to 69×10^9/L between day 1 and day 3 in our patient. Tamoxifen either alone or given concurrently with chemotherapy may increase the risk of thrombosis. Our patient presented with clumps on day 2. Even though our patient experienced liver hematoma on tamoxifen, studies have shown that the concurrent use of tamoxifen with direct anticoagulants showed a similar risk compared with aromatase inhibitors.

Keywords: Tamoxifen, Breast cancer, Liver hematoma, Thrombocytopenia, Invasive ductal carcinoma

INTRODUCTION

Tamoxifen is a non-steroidal selective estrogen receptor modulator that is used in the adjuvant therapy of premenopausal breast cancer patients and neoadjuvant therapy of low-risk stages of postmenopausal breast cancer patients.[1] Tamoxifen can exert an estrogenic or anti-estrogenic effect in different tissues. Tamoxifen acts as an agonist to estrogen receptors in the uterine endometrium, bone tissue and coagulation system; however, it acts as an antagonist in breast tissue.[2] Binding of tamoxifen to the estrogen receptor triggers a conformational change in the receptor which leads to a cascade of intracellular signals that alters gene expression of estrogen-regulated genes. The mechanism for its anti-neoplastic effects is through the induction of apoptosis through the activation of caspase-3 and JNK-1 pathways.[3] Tamoxifen is a prodrug which is primarily metabolized by the hepatic enzyme: CYP2D6 to generate the major active metabolites (4-hydroxytamoxifen and endoxifen) that exert its therapeutic effects.[4] Tamoxifen is orally administered and metabolized by hepatic cytochrome enzymes and has a half-life of 5 -7 days.[5]

CASE REPORT

A 44-year-old African American female with a previous medical history of major depressive disorder presented to the hospital with a dense feeling on her right breast following self-examination. A bilateral breast ultrasound

revealed a 1.7 cm irregular mass in the right breast at 10 o'clock position in the middle depth, raising suspicion for malignancy. The patient was on trazodone HCL (100 mg/day) oral tablet due to the major depressive disorder.

The patient underwent a right breast lumpectomy, and the pathology report revealed the diagnosis of an invasive ductal carcinoma (ER+, PR+ and HER2-) of the right breast with no lymphatic or vascular invasion and 0/1 lymph node positivity. The patient underwent chemotherapy with doxorubicin and cyclophosphamide (AC×4) and subsequently received pegfilgrastim the day after chemotherapy. In addition, chemotherapy with paclitaxel was started and completed.

Nine months after diagnosis, a combination of local radiotherapy with chemotherapy with tamoxifen (20mg tablet /day) was started. Two months post tamoxifen initiation, the patient presented at the hospital with right upper quadrant abdominal pain with sharp and stabbing characteristics, radiating to the right shoulder. The pain was associated with nausea and vomiting. Abdominal/pelvic CT with contrast revealed that the patient developed a 25×58×85 mm subcapsular hematoma of the right anterior lobe of the liver with a grade 2 laceration, and a dilation of the left gonadal vein and anterior fundal hematoma (Figure 1 A). Consequently, the patient was hospitalized, and tamoxifen was stopped.

The PET/CT scan performed one month later revealed that the hematoma and the previously noted collection of fluid in the right breast has resolved (Figure 1 B). In addition, interval decrease in the intensity of the hypermetabolic activity in the soft tissue changes in the right lateral breast was noted.

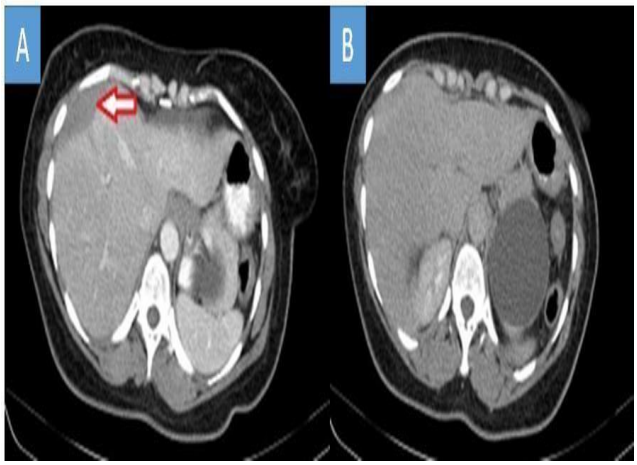

Figure 1 (A and B): Abdominal CT imaging, arrow showing liver hematoma following administration of tamoxifen. Resolution of the hematoma after the cessation of tamoxifen therapy.

Additionally, the patient developed thrombocytopenia, likely due to the administration of tamoxifen in combination with radiotherapy (Table 1). Tamoxifen was stopped and the patient was started on exemestane but developed multiple side effects such as joint pain, hot flashes, blurry vision.

Table 1: Blood picture showing the platelet levels, prothrombin time, INR, and PTT following tamoxifen administration.

Variables	Reference range	Day 1, 16:13	Day 1, 21:00	Day 2, 05:30	Day 2, 11:20	Day 2, 19:45	Day 3, 05:25
Platelets	130-450×10^9/l	139	137	Clumps	94 (Low)	69 (Low)	89
Prothrombin time	9.2-12.8 seconds	11.7					
INR	0.7-1.2	1.1					
PTT	23.5-35.5 seconds	27.9					

DISCUSSION

Our case suggests the development of liver hematoma with thrombocytopenia associated with tamoxifen therapy. Tamoxifen can cause liver injury through the following mechanisms: by accumulating in the mitochondria and inhibiting the mitochondrial fatty acid beta-oxidation, inhibiting oxidative phosphorylation, causing the leakage of electrons from the electron transport chain, increasing the production of reactive oxygen species.[5]

Tamoxifen has been the standard adjuvant hormonal therapy in premenopausal and post-menopausal women with ER-positive breast cancer who have already undergone surgery. Adjuvant use of tamoxifen for 5 years was shown to safely reduce 15-year risk of breast cancer recurrence and death by a third, irrespective of progesterone receptor status, age, nodal status, or chemotherapy use.[6] However, in ER-negative disease, adjuvant tamoxifen has little to no effect on the disease recurrence and mortality.

Following tamoxifen administration, there was a significant drop in the platelet count from 139×10^9/l to 69×10^9/l between day 1 and day 3 in our patient (Table 1). This significant drop in platelet count may be due to platelet consumption due to the formation of clumps following the treatment with tamoxifen as well as due to tamoxifen mediated. Tamoxifen either alone or given concurrently with chemotherapy was shown to increase the risk of thrombosis 7. It was shown that patients

receiving adjuvant treatment with tamoxifen have a 2.5 times higher risk of thrombosis.[7] Our patient presented with clumps on day 2 as shown in Table 1. Even though our patient experienced liver hematoma on tamoxifen, studies have shown that the concurrent use of tamoxifen with direct anticoagulants showed similar risk compared with aromatase inhibitors.[8]

Tamoxifen, a selective estrogen receptor modulator, has been shown to cause increased platelet nitric oxide and reduced peroxynitrite, therefore resulting in impaired platelet function.[3] Concurrent use of selective serotonin receptor inhibitors (SSRI) and tamoxifen can lead to competitive or direct inhibition of metabolism of tamoxifen.[2] Consequently, this may lead to reduction in the plasma concentration of the endoxifen (a metabolite of tamoxifen). On the other hand, intermediate concentration of endoxifen in the serum have been observed in women taking the weaker CYP2D6 inhibitors (sertraline and citalopram) along with tamoxifen treatment.[2] While our patient was taking trazodone for treatment of major depressive, studies have shown that trazodone has no effect on the inhibition of CYP2D6, therefore does not affect the metabolism of tamoxifen.[8]

CONCLUSION

We presented a case of thrombocytopenia and liver hematoma two months after the start of tamoxifen treatment in a patient with invasive ductal carcinoma that resolved after the cessation of tamoxifen therapy.

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