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# Intervention by clinical pharmacist targeting Nonalcoholic Steatohepatitis induced by Tamoxifen

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**ABSTRACT**

A 48- year-old female patient, morphologically confirmed with unilateral left breast carcinoma two years ago, has been on maintenance therapy with tamoxifen. Recently, the patient presented with complaints of fatigue, right upper quadrant pain and back pain. These symptoms raised concerns about hepatic damage. Subsequent investigations revealed elevated hepatic enzymes. Neither the patient nor her family members have a history of hepatic dysfunction. Consequently, tamoxifen induced injury was suspected due to the absence of other apparent causes. Careful follow- up and a timely change of therapy prevented the occurrence of further serious adverse events.

## INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is a catch-all name for a number of liver disorders that can affect people who consume little to no alcohol. Nonalcoholic steatohepatitis (NASH), an aggressive form of fatty liver disease that is characterized by liver inflammation and may progress to advanced scarring (cirrhosis) and liver failure, can be developed in some people with NAFLD [1]. Age, ethnicity, genetics, and the presence of co morbidities (such as obesity, type 2 diabetes, and hypertension) were all linked to the risk of this illness development [2]. NASH may also be linked with some medications including tamoxifen. NASH in patients receiving tamoxifen was observed in early case reports and limited series [3].

For pre menopausal patients with estrogen receptor (ER)-positive breast cancer, the selective estrogen receptor modulator (SERM) tamoxifen is a well-known adjuvant endocrine therapy.Tamoxifen use in ER-positive patients is advised for a minimum of five years due to the drug's ability to improve patient survival rates. Vaginal hemorrhage, endometrial cancer, deep vein thrombosis, pulmonary embolism, and fatty liver are just a few of the negative effects associated with long-term tamoxifen use that have been documented. Among these fatty liver is a significant adverse effects of tamoxifen. The development of hepatic steatosis in 43% of tamoxifen-treated breast cancer patients was also noted within the first two years of their treatment.

Similar to tamoxifen, aromatase inhibitors (AI) work by preventing the effects of estrogen. But AI does not significantly increase the prevalence of fatty liver, unlike tamoxifen [4]. Nonsteroidal aromatase inhibitor letrozole is frequently used to treat breast cancer. The enzyme aromatase transforms androstenedione and testosterone into estrone. The ovary and placenta, contain the highest concentrations of aromatasin premenopausal women. Although in smaller amounts, aromatase is also present in other tissues like the liver, kidney, adrenals, brain, muscle, and subcutaneous fat where it is also involved in the synthesis of estrogens. In postmenopausal women, these tissues are the main source of estrogen. Inhibitors of aromatase

were created as an antiestrogen treatment for breast cancer in postmenopausal women by preventing the synthesis of estrogen in peripheral tissues.There aren't many published cases of letrozole therapy for a long time causing clinically obvious liver damage. Letrozole, unlike tamoxifen, has not been linked to the onset of steatohepatitis or fatty liver disease [5].

Adjuvant treatment with letrozole, as opposed to tamoxifen, decreased the incidence of recurrent illness, especially at distant sites, in postmenopausal women with endocrine-responsive breast cancer [6].

## CASE REPORT

A 48-year-old female patient was histopathologically diagnosed with unilateral left breast carcinoma two years ago. The breast cancer tissue was human estrogen and progesterone-positive. She underwent neoadjuvant chemotherapy with 4 cycles of the AC regimen, followed by 4 cycles of docetaxel. She subsequently underwent mastectomy and radiation therapy and is currently on maintenance therapy with tamoxifen 20mg daily. Her blood enzymes were normal prior to starting tamoxifen [Table No:-1], but after the course of a year, they were discovered to be high. She explicitly denied experiencing nausea, lethargy, or abdominal discomfort as signs of liver illness. She denied ever drinking alcohol and had no major history of liver problems. She was not taking any other medications, and she had no risk factors for viral hepatitis. A physical examination revealed no signs of fever, rash, stomach pain, or liver or spleen enlargement. Despite having a body mass index of 27.9, suggesting she was overweight, she hadn't put on any weight in the previous 12 months.

Patient now presented with fatigue, right upper quadrant pain and back pain. These symptoms indicated hepatic damage and further investigations were ordered upon which the USG abdomen scan revealed hepatomegaly with grade III fatty changes and fibroscan examination also supported the liver injury with a median stiffness of 20Kpa. Serum aminotransferase values were moderately elevated (ALT 55 U/L, AST 48 U/L) and alkaline phosphatase (170 U/L) value was also high. Whereas bilirubin (0.5 mg/dL), albumin (3.8 g/dL), and prothrombin time (INR 1.1) were all within the normal ranges. Glucose and cholesterol levels during fasting state were normal. Both autoantibodies and hepatitis A, B, and C tests came out negative. Serological testing was also done showing HSV - 1 and HSV - 2 negative. A vitamin supplement containing the combination of omega - 3 - fatty acid and vitamin E and PPAR agonist saroglitazar were given. Tamoxifen was discontinued for now as per the call of clinical pharmacist as it worsens liver damage and the patient was ordered for hormone (FSH and Estradiol) test.

## DISCUSSION

Up to one-third of women on tamoxifen may develop fatty liver, however this condition is typically benign and not accompanied by elevated serum enzyme levels, symptoms, or the progression of liver disease. However, in some cases, the buildup of fat is linked to the development of inflammation and cell damage (steatohepatitis), which can result in fibrosis and, in the long run, cirrhosis. In most cases, serum aminotransferase levels are just slightly increased [7]. In this instance, cessation of tamoxifen led to a gradual improvement in serum enzymes [4].

Prospective investigations in Asian populations showed that within 2 years of the commencement of treatment, more than 30% of the patients had hepatic steatosis associated to tamoxifen[8].

The exact mechanism through which tamoxifen results in fatty liver is not fully elucidated. The "multiple hit" concept, which contends that liver would become more susceptible to oxidants as fat built up, might then promote the development of steatohepatitis by subsequent hits (such as tamoxifen), is the most prevalent theory [4]. Reactive oxygen species (ROS) and decreased mitochondrial oxidation of fatty acids have both been linked to the hepatotoxicity of tamoxifen. The mitochondria are negatively affected by tamoxifen in a number of ways, including decreased phosphorylation efficiency, compromised electron transfer along the electron transport chain, and compromised mitochondrial membrane integrity. These consequences result in mitochondrial malfunction and an increase in the generation of ROS [9].

All of these causes linked tamoxifen to several cases of toxic hepatitis, extensive hepatic steatosis, multifocal hepatic fatty infiltration, submassive hepatic necrosis, and even human cirrhosis. Other long term adverse effects include vaginal bleeding, endometrial cancer, deep vein thrombosis, pulmonary embolism, etc. Preventing serious long-term adverse effects like fatty liver disease is crucial because the majority of patients with early-stage breast cancer have a favorable prognosis. The therapeutic effects of Osthole, isolated from medicinal plants especially Fructus Cnidii, on tamoxifen-induced acute liver injury in mice was studied. A pretreatment with osthole considerably reduced the tamoxifen-induced elevations in serum

**Table 1 :** Liver Function Test before and after Tamoxifen Therapy

| TIME AFTER STARTING TAMOXIFEN | ALT (U/L) | AST (U/L) | ALP (U/L) | BILIRUBIN (mg/dL) | OTHERS |
|---|---|---|---|---|---|
| Pre | 22 | 27 | 57 | 0.5 | 1 month before surgery |
| 13 months | 44 | 37 | 143 | 0.5 | Regular checking |
| 19 months | 49 | 41 | 158 | 0.6 | |
| 25 months | 55 | 48 | 170 | 0.7 | Tamoxifen Stopped |

ALT and AST activity in the current investigation [8].

As clinical pharmacists, we have recognized the exhibited symptoms and heightened liver enzymes to be a result of tamoxifen usage. Therefore, we recommended discontinuing this causative treatment and substituting it with a more effective and less liver-damaging medication, namely letrozole. Additionally, considering the patient's approach towards menopause, the adoption of this drug is even more suitable.

The nonsteroidal third - generation aromatase inhibitor letrozole was approved in 1997 in the US for postmenopausal women with estrogen receptor positive breast cancer. It's used as adjuvant therapy and as a first-line treatment for advanced breast cancer. It's available in generic forms as well as under the brand name Fempro, with a recommended daily dose of 2.5 mg tablet for up to five years.In contrast to tamoxifen's competitive binding to the estrogen receptor to inhibit estrogen activity, aromatase inhibitors work by stopping the conversion of androgens to estrogens, thus reducing estrogen levels in tissue and plasma.

For instance, letrozole as a first-line treatment for metastatic breast cancer led to notably higher response rates, longer progression-free periods, and significant improvements in one- and two-year survival rates when compared to tamoxifen. Additionally, letrozole showed promise as extended adjuvant therapy for women who had early-stage breast cancer and were disease-free following five years of initial tamoxifen treatment, resulting in improved disease-free survival. In the context of neoadjuvant therapy, letrozole outperformed tamoxifen.

## CONCLUSION

In conclusion, the case report highlights the potential risk of tamoxifen-induced Non-alcoholic Steatohepatitis (NASH), shedding light on the importance of monitoring liver function in patients undergoing tamoxifen therapy. The clinical pharmacist's intervention involving the switch to letrozole demonstrates the role of personalized treatment adjustments in minimizing adverse effects. Further research is warranted to better understand the underlying mechanisms and to determine the prevalence of this potential adverse effect. Careful assessment of the risk-benefit profile of tamoxifen and close collaboration between oncologists and hepatologists are essential in managing such cases effectively.

## LIMITATION

Unfortunately, ongoing patient follow-up remained out of reach.

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## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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