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Case Report

Oncology Section

Tamoxifen Induced Pancreatitis: An Unusual Complication of Commonly used Drug

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ABSTRACT

Tamoxifen is a selective oestrogen receptor modulator used for the treatment of oestrogen/progesterone receptor positive breast cancer. It possess antagonistic or agonistic activity depending on the tissue location i.e., antagonistic action on breast but agonist action on endometrium and bones. The side effects of tamoxifen include hot flushes, gynaecologic symptoms (vaginal dryness, vaginal discharge), depression, forgetfulness, sleep alterations, weight gain, alteration of lipoprotein metabolism, thromboembolic disorder. Tamoxifen, like oestrogens, increases the plasma level of triglycerides and liver secretion of Very Low Density Lipoprotein (VLDL). Moreover, it inhibits the key enzymes of triglyceride metabolism. However, there are few cases of severe tamoxifen induced hypertriglyceridemia and pancreatitis. Hypertriglyceridemia is one of the risk factor for acute pancreatitis.

Here we present a case of tamoxifen-induced hypertriglyceridemia and acute pancreatitis in a 50-year-old female without any comorbidity. She was treated with supportive antibiotics and supportive therapy. About one week after discharge, patient was started on letrozole 2.5 mg once a day. Clinicians must be aware of this rare side effect of tamoxifen, so baseline and periodic testing of triglyceride level must be done to avoid such complications.

Keywords: Carcinoma breast, Hypertriglyceridemia, Letrozole

CASE REPORT

A 50-year-old post-menopausal female patient with no comorbidity presented to the Medical Oncology Department in December 2016 with complaints of abdominal pain and vomiting prior to 3 days of presentation. Patient was a known case of carcinoma right breast since six months of this episode. She had underwent right Modified Radical Mastectomy (MRM) in January 2016 and the histopathologic examination was suggestive of invasive ductal carcinoma {pT2N2M0 (Stage IIIa)}. Her hormonal status was oestrogen and progesterone receptor positive and Her 2 neu receptor was negative(ER + and PR+ and Her 2 neu -). She was given chemotherapy involving 4 cycles of Injection adriamycin (60 mg/m2) and Injection cyclophosphamide (600 mg/m2) (AC) combination three weekly followed by four cycles of single agent Injection paclitaxel (175 mg/m^2) three weekly followed by Postoperative Radiotherapy (PORT). After fifteen days of completion of post operative radiotherapy patient was started on tablet tamoxifen (20 mg per day) orally. Within one month of starting tamoxifen patient developed above symptoms. Patient was admitted and underwent investigation like CBC, LFT, RFT, serum electrolytes were within normal limits. Ionized serum Calcium was low 7 mg/dl. Ultrasound of abdomen and pelvis was suggestive of bulky pancreas. Serum amylase and serum lipase were done which were more than three times elevated (280 mg/dl and 350 mg/dl respectively).

As the patient had no history of substance abuse and USG did not show any presence of cholelithiasis, serum lipid profile was done which showed elevation of serum triglyceride levels i.e., 1050 mg/dl (Normal levels 30-150 mg/dl), the rest lipid profile was within normal limits.

On clinical and laboratory suspicion of drug induced acute pancreatitis, patient was kept nil by mouth and Ryles tube insertion was done. Patient was started on intravenous pantoprazole, tramadol. After three to four days of symptomatic management patient was started on oral sips and later on soft diet.

After period of two weeks patient's pain had relieved completely and was taking food orally. The serum lipid profile was repeated which showed normal serum triglyceride i.e., 100 mg/dl and rest of lipid profile was within normal limits. The serum lipase and amylase were also within normal limits during this time. So she was discharged and asked to follow up after one week. One week after discharge she was started on tablet letrozole 2.5 mg once a day.

So, the above findings and lab parameters confirmed that tamoxifen caused acute elevation of serum triglycerides and precipitation of acute pancreatitis, since the levels of triglycerides and serum lipase and amylase became normal after weeks of stopping tamoxifen.

DISCUSSION

Acute pancreatitis is an acute inflammatory process involving the pancreas. It can exhibit a wide spectrum as mild interstitial pancreatitis to severe pancreatitis with pancreatic necrosis and multi-organ failure as continum. Most cases are related to gallstones or heavy alcohol intake, abdominal trauma, drugs, vasculitis, viral infection, peritoneal dialysis, cardiopulmonary bypass and Endoscopic Retrograde Cholangiopancreatography (ERCP) [1].

Drug induced pancreatitis is rare with incidence between 2% to 5%. Drugs implicated in causation of acute pancreatitis include azathioprine, mercaptopurine, asparaginase, tetracyclines, oestrogens, sulphonamides, thiazides, furosemide and glucocorticoids [2].

Generally account for drug induced pancreatitis comes from many anecdotal reports. Drug induced pancreatitis is rarely associated with features of drug reaction such as rash, lymphadenopathy, eosinophilia. Drug induced pancreatitis occurs within four to eight weeks of starting therapy. Several mechanism leading to drug induced pancreatic injury have been elucidated which are as follows [3].

Hypersensitivity Reaction: Most common and significant which occurs within four to eight weeks of starting therapy (metronidazole, aminosalicyclates, and tetracycline)

Accumulation Of Toxic Metabolite: It causes pancreatic injury months after the start of medication (valproic acid, diadinosine (DDI). Notable examples being drugs inducing hypertriglyceridemia (e.g., thiazides, tamoxifen, isotretinoin).

Intrinsic Activity: It causes pancreatic injury in case of overdosage (e.g., acetaminophen, erythromycin).

Possible intermediary event leading to tamoxifen induced pancreatitis is hypertriglyceridemia (a well-known risk factor for acute pancreatitis). However, answer to the question, how elevated triglycerides cause pancreatic injury is still unclear. Few theories which has been postulated to explain this phenomenon are as follows [4]:

1. Impaired clearance of chylomicrons leads to the obstruction of capillaries which leads to pancreatic ischemia.
2. Pancreatic lipase causes hydrolysis of excess of triglycerides to free fatty acids that induce inflammatory changes.

Tamoxifen induced acute pancreatitis is typically associated with triglyceride level of more than 1000 mg/dl and pancreatic injury recurs within several months of drug rechallenge [5]. One of the important aspect of hypertriglyceridemia induced acute pancreatitis is that the serum amylase level can be normal which can easily misled the clinicians regarding the diagnosis of pancreatitis.

Tamoxifen exhibits antagonistic and agonistic activity on oestrogen receptor. Its influence on lipid metabolism is determined by agonistic effect [6]. Tamoxifen and the oestrogens leads to hypertriglyceridemia due to the following mechanism [6]:

1. By the virtue of their agonistic activity on oestrogen receptor, increases the plasma level of triglycerides and liver secretion of the main carrier of TG i.e., VLDL
2. Tamoxifen inhibits the key enzymes of triglyceride metabolism by decreasing the activity of lipoprotein lipase and hepatic triglyceride lipase.

Though various trials report only modest increase in serum triglycerides levels, however severe increase in triglycerides can also occur [7,8]. As the removal of triglycerides is a saturable process, patients with pre-existing hypertriglyceridemia may be near the point of saturation before staritng tamoxifen. Once treatment is initiated, the removal mechanism is saturated and large increases in lipid levels may occur. It is more probable to induce very high triglycerides levels in patients with a history of dyslipidaemia.

Serial No.	Authors	Comorbidity	Duration	Outcome
1.	Noguchi M et al., [9]	Not Available	7 months	Death
2.	Colls BM and George PM [10]	Dyslipidemia	Not available	Favourable
3.	Elisaf MS et al., [1]	Dyslipidemia	8 months	Favourable
4.	Artac M [11]	DM	12 months	Favourable
5.	Lin HH et al., [2]	Not Available	24 months	Favourable
6.	Alagozlu H et al., [12]	Dyslipidemia	12 months	Favourable
7.	Sakhri J et al., [13]	No	12 months	Favourable
8.	Kim YA et al., [14]	DM	3 months	Favourable
9.	Czyzykowski R et al., [15]	Dyslipidemia	9 months	Favourable
10.	Present	NO	1 months	Favourable

[Table/Fig-1]: Chart depicting different reported cases with tamoxifen-induced pancreatitis.

Our patient was a case carcinoma breast with ER positive breast cancer and was started on adjuvant hormonal therapy with tamoxifen. After completion of chemotherapy as patient being menopausal, was started on tamoxifen. Within six months of starting tamoxifen patient developed abdominal pain and was diagnosed with acute pancreatitis based on serum lipase and amylase levels. Further, test to look for most causes revealed normal reports. However, lipid profile was consistent with hypertriglyceridemia in absence of previous dyslipidemia.

Most case reported in literature developed delayed hypertriglyceridemia induced pancreatitis or had predisposing dyslipidemia or Diabetes mellitus [Table/Fig-1]. Only one case report showed early onset pancreatitis within three months of starting the drug [Table/Fig-1].

CONCLUSION

Tamoxifen induced pancreatitis is a rare phenomenon and this side effect must be borne in mind while patient is being considered for this drug. As tamoxifen is being used very commonly in ER and PR positive breast cancer patients in pre and post menopausal state, many females are at risk of developing this side effect. It also leads to greater morbidity and delays in treatment. Care has to be taken while using tamoxifen especially in previously diabetic and hypertriglyceridemic females.

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