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CLINICAL VIGNETTE

Acute Pancreatitis Secondary to Tamoxifen-Induced Hypertriglyceridemia

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Introduction

Acute pancreatitis is a potentially life threatening inflammatory disease that affects approximately 40 adults per 100,000 each year in the United States.[1,2] While gallstones (~40-70%) and alcohol use disorder (~25-35%) are the two most common causes, other known etiologies include hypertriglyceridemia, more than 100 drugs, endoscopic retrograde cholangiopancreatography, and scorpion bites.[1,3,4] Hypertriglyceridemia, typically with very high, >500 mg/dL triglycerides, is a rare but well documented cause of acute pancreatitis associated with higher morbidity and mortality than other etiologies of pancreatitis.[1,2,4,5] Tamoxifen is a selective estrogen receptor modulator commonly used as adjuvant hormonal treatment in post-operative breast cancer since the 1970s that has been identified as an uncommon but known cause of hypertriglyceridemia-induced acute pancreatitis.[3,6,7] This report highlights a case of acute pancreatitis caused by hypertriglyceridemia secondary to tamoxifen use and proposes possible screening steps and management strategies.

Case Summary

A 47-year-old woman with a history of stage II left breast cancer status post bilateral mastectomy and reconstruction on adjuvant tamoxifen presented with three days of abdominal pain, nausea, and oral intolerance. Her abdominal pain was severe, cramping epigastric and left upper quadrant radiating to her back. Her family history was notable for maternal hyperlipidemia and hypertriglyceridemia. She was afebrile, tachycardic, and normotensive with left upper quadrant tenderness to palpation. Labs were notable for a WBC of 14, lipase of 114, and triglycerides of 982 mg/dL, previously ~200 mg/dL three years prior. The remainder of her CBC and metabolic panel were within normal range. CT abdomen pelvis in the ED demonstrated extensive peripancreatic stranding and a small non-drainable crescentic fluid collection without evidence of necrosis, consistent with acute pancreatitis. She was initially managed with bowel rest and IV fluid hydration. Tamoxifen, which was started three months prior to admission, was held, due to concerns regarding its role in causing her new hypertriglyceridemia. With IV fluid resuscitation, her abdominal pain improved and triglycerides improved to a nadir of 409 mg/dL. However, once her diet was liberalized, despite complete resolution of abdominal pain, she began to have loose stools ~10-15/day and fasting triglyceride levels ~500 mg/dL. Clostridium difficile testing was negative and she was started on pancrealipase with resolution of the diarrhea. Endocrinology assisted with an insulin drip and she was started on daily fenofibrate 130 mg. Triglyceride levels remained in the mid-500s mg/dL, and she was started on fish oil 2g BID. Once she had achieved good oral tolerance, stable fasting triglycerides, and completely resolved abdominal symptoms, she was discharged on a very low-fat diet with the addition of atorvastatin 40mg daily and planned outpatient lipid clinic follow up. One month post-discharge, her fasting triglyceride levels was 180 mg/dL and she was transitioned from tamoxifen to anastrozole.

Discussion

Acute pancreatitis secondary to severe hypertriglyceridemia is associated with generally poorer outcomes than other causes of acute pancreatitis due to increased inflammation, oxidative stress, and endothelial dysfunction.[2-5] The mechanism by which hypertriglyceridemia causes such severe pancreatitis is presumed to be due to the release of harmful free fatty acids (FFA) from the hydrolysis of triglycerides by pancreatic lipase in exocrine pancreatic acinar cells, leading to ischemia and pancreatic cell injury.[1,2,4] The release of these predominantly unsaturated fatty acids causes an inflammatory cascade, imbalance of vasoactive factors, and cytosolic calcium overload with endoplasmic reticulum stress resulting in direct cytotoxic effects on pancreatic acinar and vascular endothelial cells.[1,3] This results in associated increased oxidative stress, vascular permeability, intravascular coagulation, activation of proteases and trypsin causing pancreatic auto-digestion, ischemia, and acinar necrosis.[1,3] The risk of pancreatitis is highest in patients with triglycerides >1000mg/dL but can occur if triglycerides exceed 500mg/dL.[2,4] It is crucial to measure serum triglycerides as soon as possible after symptom onset as levels can decrease rapidly with fasting due to residual lipoprotein lipase (LPL) activity and with supportive treatment of pancreatitis.[4,5]

These devastating levels of triglycerides can be due to primary hypertriglyceridemia from genetic and environmental factors as well as secondary causes, including metabolic syndrome, poorly controlled diabetes, alcohol use, pregnancy, and medications such as tamoxifen, estrogens, corticosteroids, retinoids, and atypical antipsychotics.[1,3,4] Tamoxifen is a non-steroidal selective estrogen receptor modulator that competitively binds to estrogen receptors on tumor cells and is a mainstay of adjuvant therapy in hormone-dependent breast cancers.[3,6,7] While tamoxifen has an overall favorable effect on the lipid profile, including decreased total cholesterol, low-density lipoprotein

(LDL), and Apo A and B, resulting in a decreased risk of myocardial infarction, it is known to have a higher risk of hypertriglyceridemia, likely due to its partial estrogen agonism. Tamoxifen's agonism on estrogen receptors leads to increased VLDL (very low-density lipoprotein) secretion from the liver and decreased activity of LPL, a key enzyme in capillary endothelial cell triglyceride metabolism, and hepatic lipase, ultimately resulting in increased circulating triglycerides.[1,3,6,8,9]

In addition to standard supportive initial treatments of acute pancreatitis, management in these cases hinges on the reduction of circulating triglycerides.[2,4,10] Although there are no established guidelines for the management of hypertriglyceridemia-induced acute pancreatitis, insulin and heparin infusions, plasma exchange, and oral lipid lowering therapies have been the mainstays of treatment, predominantly via upregulation of LPL.[2,4] Oral lipid lowering therapies including fibrates, omega-3-fatty acid, statins, and niacin, should be initiated once patients are able to tolerate oral intake and continued until triglyceride levels fall below 500mg/dL, while other preventative lifestyle strategies are employed.[1,2,4,5] Fibrates and omega-3-fatty acids are the first and second line agents with triglyceride reductions of ~36% and 25-33%, respectively, while statins induce a 10-18% reduction and niacin (Vitamin B3) reduces triglycerides by 20% but is limited by its side effect profile.[4,9,11,12] Finally, lifestyle modifications include discontinuation of any offending agents, adherence to a very low fat diet, maintaining good glycemic control, weight reduction and increased physical activity, and eliminating alcohol.[1,2,4,5]

Conclusion

This case is an excellent example of acute pancreatitis caused by a combination of primary and secondary etiologies of hypertriglyceridemia. Given her personal and family history of hyperlipidemia and hypertriglyceridemia, this patient was at elevated risk and likely suffered from acute pancreatitis due to an exacerbation of her hypertriglyceridemia by tamoxifen use. This case demonstrates the importance of screening for any personal or family history of hypertriglyceridemia prior to initiation of tamoxifen with close monitoring in the presence of risk factors. Aromatase inhibitors can be considered an alternate strategy for the adjunctive treatment of hormone-responsive breast cancers in cases in which hypertriglyceridemia is a significant concern.

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