CLINICAL VIGNETTE

Testosterone Induced Acute Pancreatitis in a Transgender Patient Undergoing Gender Affirming Medical Care

Jason Bahk, MD, FACP and Sewon Oum, MD

Introduction

Advances in medical and surgical treatments for gender dysphoria need increasing clinical awareness of the risk and benefits of treatment.[1] What is not well documented is incidence and risk factors with the use of sex hormones, specifically testosterone, including risk of hormone induced acute pancreatitis. Information on testosterone induced pancreatitis is mostly in the athletic performance enhancing drug (PED) literature.[2] This male patient, born biologically female, recently started testosterone cypionate treatment for gender dysphoria and presented with testosterone induced acute pancreatitis in the setting of morbid obesity and hypertriglyceridemia.

Case Presentation

This is a 44-year-old male, female to male transgender morbidly obese patient with gender dysphoria who presented with acute onset abdominal pain and leukocytosis to 20,300. Past medical history includes BMI of 44, hypertriglyceridemia and resected thyroid carcinoma. The patient was started on testosterone cypionate injections 30 milligrams/weekly, three weeks prior. Three days prior to admission he developed sudden onset of abdominal pain described as mid-epigastric, persistent, with ten out of ten severity and oral intolerance. The pain is sharp, stabbing and radiates to the back and worsens with eating. He notes only minimal improvement when not eating. On admission, the patient's vitals were unremarkable with the exception of mild sinus tachycardia in the low 100s. Serum lipase in the emergency department was 916. There was no recent travel, no scorpion exposure, no alcohol or drug use other than prescribed medications. His medical record noted remote history of hypertriglyceridemia. Family history was negative for any significant cases of pancreatitis and or other gastroenterological issues and diseases.

The patient was made NPO, and started on aggressive intravenous (IV) fluid hydration with normal saline, IV hydromorphone for pain, and prescribed pancreas rest with advancement of diet as tolerated. Initial blood cultures were negative. Computed tomography of the abdomen showed diffuse edema surrounding the entire pancreas that was suspicious for acute pancreatitis, but without phlegmon, abscess formation, necrosis, or pseudocyst formation. The CT scan showed some fatty infiltration of the liver but no cirrhosis, and no biliary ductal dilatation. A follow-up MRI did not show choledocholithiasis or pericholecystic fluid. Other than findings of acute pancreatitis, there was no ductal dilatation or other acute intra-abdominal pathology. His Ranson criteria was 1/8 with leukocytosis above 16,000 cells/$mm^{3.}$ This predicts a 2% mortality (0-2, 2% mortality, 3-4% 15% mortality, 5-6 40% mortality, and 7-8 100% mortality).[3]

IgG4 levels and serum triglycerides on admission were unremarkable. Hereditary pancreatitis gene panel was not sent due to the lack of family history, with availability of extensive family history given.

Discussion

The majority of acute pancreatitis cases in the United States are due to chronic alcohol use and hepatobiliary obstruction from gallstones.[4] Drug induced pancreatitis represents 0.1 to 2% of cases. The most common drugs are azathioprine, sulfasalazine, mesalamine, simvastatin, and metronidazole.[4] Drug induced pancreatitis is often difficult to diagnose and is almost always diagnosed due to a temporal relation from drug administration once alcohol and gallstones are ruled out as causes.[4,5] Table 1 shows a classification of evidence for drug induced reactions, including but not limited to drug induced pancreatitis, described by Karch in 1975. This continues to be used to establish drug side effects.[5]

Once alcohol and gallstone etiologies for pancreatitis are ruled out, a thorough and comprehensive history is needed to diagnose drug induced pancreatitis.[4] Should potential medication be deemed necessary by the patient and clinician, re-challenge can be considered based on necessity and patient preference, preferably at lower doses.[4] Between biologic males and female there appear to be no difference in the rates of medication-induced acute pancreatitis. However, between genders, there appears to be a difference between biologic males and female in hypertriglyceridemia induced subtype of acute pancreatitis, with two thirds of the cases reported in men. It is thought that this may be due to higher endogenous levels of testosterone in biologic males.[6]

One animal trial, examining pancreatic parenchyma, found concurrent consumption of a high fatty diet (HFD) and testosterone cypionate produced significant beta islet changes and gene expressions in multiple metabolic pathways, with increased exocrine activity noted in rats.[7] Gonclaves et. al, fed female rats testosterone cypionate and high fatty lipid diets to evaluate the impact on the pancreas. Other arms of the study included testosterone only and the control arm. The HFD was composed of mostly hydrogenated fats, attempting to replicate a highly processed foods. The combination of the HFD and testosterone cypionate lead to multiorgan dysfunction, and most importantly showed microstructural adaptations in the pancreas.[7] The authors surmise that a combination of HFA and testosterone exposure lead to higher rates of pancreatic exocrine activity than either alone. This outcome infers that a premature exocrine release of lytic enzymes in the pancreas as a result of the concurrent HFD and testosterone administration leads to increased acute pancreatitis in the rat study population.[7]

A review by Jones et. al. examined cases of androgenous hormone induced pancreatitis and reported interstitial edematous sub-type was the most common and rarely presented with severe necrosis, morbidity and mortality. They often rapidly improve and resolve after stopping the androgen.[3] Consistent with the rat study, it appears the risk of sex hormone induced acute pancreatitis is higher in patients with concurrent hypertriglyceridemia.[3]

Current medical management of female to male transition uses testosterone to induce virilization.[1] Both surgical and medical management options exist. Medical hormonal management is often started prior to plans for surgical correction. Current European standards recommend 200-250 mg of intramuscular testosterone cypionate.[3] There is limited information regarding the risk of acute pancreatitis in patients with existing hypertriglyceridemia, with no recommendations for a screening lipid panel and serum triglyceride level prior to initiating testosterone treatment.[3]

There is also limited information regarding dose adjustments with only one basic animal science study reporting a dose response curve that directly correlates with the degree of pancreatitis among the rats, with no known human studies.[8] Based on the lack of a class effect and one study reporting a dose response effect with increasing risk, future guidelines may consider risk factor screening or dose reduction in high risk patients prior to starting hormone therapy for gender dysphoria patients.

Conclusion

Most case reports regarding testosterone induced acute pancreatitis are from the performance enhancing drug (PEDs) literature. They include body-building and military communities and often include other PEDs. They also include both testosterone propionate and enanthate, which often are included in a multidrug cocktail.[2] We found no cases reporting monotherapy testosterone induced acute pancreatitis in a biologic female patient undergoing hormonal therapy for gender dysphoria.[9]

The acute pancreatitis quickly resolved after stopping testosterone. He was recommended to follow-up with his primary care physician to discuss other options to manage gender dysphoria, including surgical treatment, dose reduction, and re-trial of testosterone cypionate. He was discharged home with recommendations to remain off testosterone until follow-up discussions with his primary care provider and endocrinologist.

It may be prudent to modify guidelines for hormonal therapy management. Both dose dependent recommendations and additional screening based on the patients' individual risk factors such as BMI, high fat diet intake, and hypertriglyceridemia.

Table 1. Classification of evidence adapted from and according to Karch & Lasagna.[5]

Definitely Drug Reaction	Reaction follows a reasonable temporal sequence from administration of the drug that follows a known response pattern ***Confirmed by cessation of the drug (de-challenge)*** ***Confirmed by reappearance of the symptoms upon repeated exposure to the drug (re-challenge)***
Probable Drug Reaction	Reaction follows a reasonable temporal sequence from administration of the drug that follows a known response pattern ***Confirmed by de-challenge and can not be explained by the known characteristics of the patient's clinical state***
Possible Drug Reaction	Drug reaction that follows a reasonable temporal sequence from administration of the drug that follows a known response pattern, ***but could have been produced by patient's clinical state or other modes of therapy administered to the patient***

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