

CASE REPORT**Estrogen-Induced Pancreatitis: Transgender Females at Risk**Nathan Goodwin¹, Nathaniel Nolan², Bhavana Chinnakotla³¹University of Missouri School of Medicine, Columbia, MO 65212²Department of Medicine, University of Missouri, Columbia, MO 65212³Division of Hospital Medicine, Department of Medicine, University of Missouri, Columbia, MO

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Estrogen therapy and the consideration of its potential side effects will continue to grow as the number of transgender females presenting to health care services continues to increase. The risks of estrogen therapy in this population are hard to extrapolate from previously identified data in the general population due to variation in birth sex, superior hormone doses required, and extended exposure duration that is often needed. Estrogen therapy is a rare, yet well-known, cause of acute pancreatitis with as many as 40 known reported cases in women and only one other reported case in a transgender female. The presumed mechanism is estrogen-induced hypertriglyceridemia as triglyceride levels were documented as greater than 1,000 mg/dL in most diagnosed patients. The limited data and evidence-based recommendations regarding estrogen therapy treatment and management in transgender women have led to a general lack of understanding among most practitioners. The long-term supraphysiologic doses of sex hormones required for treatment in transgender women and the dose-dependent estrogen-induced elevation in triglycerides are factors that contribute to an increased risk of pancreatitis. Therefore, the utility of regularly scheduled lipid panels in the prevention of pancreatitis increases in this population.

Keywords: latency period; supraphysiologic, screening, triglycerides

INTRODUCTION

Hormonal treatments are commonly used in the general population for indications such as menopause, contraception, and male or female hypogonadism (1). Another indication for hormone therapy is in transgender individuals transitioning to their self-identified gender (2). Many of the previously identified risks of hormonal therapy in the general population are well-documented, including the risk of

thromboembolism and the duration-dependent risk of breast cancer in women (3). However, it is difficult to extrapolate those risks to the transgender population. Transgender individuals transitioning to their self-identified gender require higher doses of hormones for extended durations (2). Studies aimed at evaluating the risk associated with hormonal treatment in the transgender population are limited and subjected to a wide variety of limitations as

they often highlight “expected” adverse drug reactions.

While the effects of estrogens on factors such as cardiovascular disease and thromboembolism in transgender females have been reported, there is little evidence in this population showing a correlation between estrogen therapy and pancreatitis. There have been over 40 reported cases (all women) in which estrogen therapy has been the causative-agent of drug-induced pancreatitis (1). To our knowledge, there is only one reported case of estrogen-induced pancreatitis in a male-to-female transgender person who was taking estrogen therapy (4). We report a case of a transgender female who developed estrogen-induced acute pancreatitis after 10 years of oral estradiol hormone therapy.

CASE REPORT

A 51-year-old Caucasian transgender female (male-to-female) presented to the emergency department with a chief complaint of epigastric abdominal pain and nausea for 4 days. She also reported anorexia with one episode of emesis and was able to tolerate only liquids. She denied diarrhea, constipation, fever and chills. She endorsed polyuria and polydipsia for about one week prior to presentation. For the previous ten years, she had been on hormone therapy consisting of oral estradiol 2mg twice daily, as well as anti-androgen therapy consisting of spironolactone 100mg daily and finasteride 5mg daily.

At the time of presentation, she denied any history of adverse side effects from her medication regimen or any recent dose adjustments. Her past medical history included gout for which she took allopurinol 300mg daily. She had no previous diagnosis of diabetes mellitus or episodes of acute pancreatitis. Her family history was significant for type 2 diabetes mellitus in her

father and was negative for hypertriglyceridemia. She denied a history of alcohol abuse, illicit drug use, or recent non-steroidal anti-inflammatory (NSAID) use. In the emergency department, physical exam revealed sinus tachycardia (102 beats/min), but vitals were otherwise within normal limits (arterial blood pressure 125/64 mmHg, respiratory rate 16 breaths per minute, temperature 36.7 degrees Celsius, SpO2 99% on room air). Her height and weight were 168 cm and 88.6 kg, respectively, with a BMI of 31 kg/m². She was in mild distress due to abdominal pain. Cardiac, lung, and neurologic exam were unremarkable. She was anicteric and non-jaundiced. She had significant tenderness to palpation in the epigastric region and left upper quadrant. No rebound tenderness or guarding were noted. Murphy’s sign was negative. Bowel sounds were normoactive. There was no costovertebral angle tenderness.

Blood tests on admission to the hospital revealed leukocytosis (17.43 x 10(9) cells/L), hyponatremia (122 mmol/L), hyperglycemia (350 mg/dL), hypocalcemia (7.8 mg/dL), elevated anion gap (26 mmol/L), elevated beta hydroxybutyrate (1.03mmol/L), and decreased CO₂ (16 mmol/L). BUN and Cr were both within normal limits, 5mg/dL and 0.59 mg/dL. Lipase was elevated (92 units/L) and alkaline phosphate level was normal (47 units/L). Both AST and ALT results were reported as “lipemic”. Urine analysis was positive for glucose (\geq 500 mg/dL), ketones (80 mg/dL), and protein (100 mg/dL) and was negative for leukocytes and nitrites.

Right upper quadrant ultrasound revealed a small fluid collection adjacent to the pancreas, consistent with a history of pancreatitis. Hepatomegaly with hepatic steatosis was also noted. There was no evidence of cholelithiasis or acute

cholecystitis. Computed tomography of the abdomen and pelvis revealed extensive fluid and fat stranding surrounding the body and tail of the pancreas, consistent with acute interstitial pancreatitis. Coarse calcifications in the region of the distal pancreatic body were also found and could indicate sequela of chronic pancreatitis versus vascular calcifications. There was no evidence of biliary duct dilation.

The patient was admitted to the progressive care unit, made nil per os (NPO), and treated with aggressive intravenous (IV) hydration with 0.9% saline at 250mL/hr for acute pancreatitis. She was started on an IV regular insulin infusion at 0.1 units/kg/hr for diabetic ketoacidosis. Hormone therapy and anti-androgens were held. Additional testing revealed a significantly elevated serum triglyceride level of 2,073 mg/dL, after which the insulin drip was increased to 0.3 units/kg/hr (9 units/hr) for the treatment of hypertriglyceridemia-induced pancreatitis. The goal triglyceride level was set at <500 mg/dL. Additionally, one day after admission, her HbA1c was found to be elevated at 10.8%. On hospital day 3, oral fenofibrate 145mg daily was added to the medical regimen for the treatment of hypertriglyceridemia. By hospital day 4, the triglyceride level had trended down to 412 mg/dL, and the anion gap had closed. The insulin drip was discontinued, and subcutaneous insulin was initiated. She was started on glargine and lispro insulin. She was also started on atorvastatin 40mg daily for further treatment of hyperlipidemia and hypertriglyceridemia. Throughout her hospitalization, the patient had refused her daily allopurinol for gout prevention and developed an acute gout flare which was treated with colchicine. By hospital day 5, the patient was tolerating a full diet. She was discharged on hospital day 7 and was

scheduled to follow-up in endocrinology clinic.

DISCUSSION

Hormone therapy for transgender patients is life-long in order to adjust and maintain their secondary sexual characteristics to more closely match their experienced gender (2). Additionally, studies have shown that there continues to be an increasing number of transgender patients who present to a wide variety of healthcare services. Now more than ever, an increased awareness of the initiation, management, and side effects of hormone therapy in the transgender population is important across a wide variety of healthcare specialties. This is especially true of estrogen hormone therapy as data from a literature review estimate that there are three times as many trans-women in the transgender population compared to trans-men (5).

Estrogen therapy, whether as oral contraception or hormone replacement therapy in post-menopausal women, is a rare, yet well-documented, cause of acute pancreatitis with as many as 40 known reported cases. The presumed mechanism is estrogen-induced hypertriglyceridemia as most reported cases document triglyceride levels greater than 1,000 mg/dL (6). Levels of this magnitude are most commonly caused by primary or genetic defects in lipid metabolism. However, other secondary causes of hypertriglyceridemia, including excessive alcohol consumption, hypothyroidism, and obesity, should be considered because treatment of each would improve the dyslipidemia (7). While 80-90% of the cases of acute pancreatitis are due to alcohol or gallstones, hypertriglyceridemia is also a well-known etiology. Reports estimate that it is responsible for up to 7% of all cases (6-8).

Estrogens cause elevations of triglyceride levels from 1.5- to 2.5-fold in a dose-dependent manner. The mechanism of estrogen-induced hypertriglyceridemia has been studied and is established (9). The risk of hypertriglyceridemia-induced acute pancreatitis is relevant with triglyceride levels greater than 500 mg/dL (6). Various authors even suggest that exogenous estrogens are relatively contraindicated when serum triglycerides are more than 300 mg/dL and absolutely contraindicated if triglyceride levels are more than 500 mg/dL (6, 7, 9). Current estrogen therapy options for the transgender population include oral estradiol, transdermal estradiol patch, and parenteral estradiol valerate or cypionate (10). Yet, there are no current international recommendations for the optimal choice of drugs, dosages, and routes despite the increasing number of transgender patients seeking hormone therapy. The limited data and evidence-based recommendations lead to a general lack of understanding among most practitioners regarding treatment and management in the transgender population.

Effective hormone treatment in transgender individuals is evidenced by suppression of endogenous sex hormone secretion determined by the person's genetic sex and maintenance of sex hormone levels within the normal range of the individual's gender identity. Estrogen therapy in transgender females is given to suppress testosterone levels into the normal range for a female. This cannot be done with physiologic doses alone, thus therapy in the transgender population often requires supraphysiologic doses of sex hormones. Because of the increased dosages required, transgender patients are at an increased risk for many of the adverse outcomes experienced by non-transgender patients undergoing hormone replacement therapy (10).

In a retrospective study, 31 women were referred to a specialty clinic for fasting plasma triglyceride levels >750 mg/dL. Of those women, 12 (39%) were taking exogenous estrogens prescribed by their physicians. Ten of them had triglyceride levels >1200 mg/dL. Four were hospitalized with severe acute pancreatitis (11). Goldenberg et al report a study involving 56 women with and without familial hypercholesterolemia who presented to their clinic with triglyceride levels >400 mg/dL and/or hypertriglyceridemic acute pancreatitis. Of those 56 women, 24 (43%) were taking hormone therapy at entry (with varying estrogen therapy regimens) and 17 (30%) had a history of acute pancreatitis. Of the 17, nine (53%) were taking hormone therapy before developing acute pancreatitis (9).

Interestingly, a study involving the largest cohort of transgender females (followed for a mean of 10 years) and estrogen therapy showed no increase in cardiovascular mortality (12). However, this should not diminish the value of lipid panels in the detection of hypertriglyceridemia both at initiation of treatment and throughout estrogen therapy in this population. A meta-analysis involving transgender patients receiving estrogen therapy found that of all parameters tested in a lipid panel, only serum triglycerides were higher at 24 months or greater (13). Also, when considering the development of hypertriglyceridemia in this patient population, latency periods have been reported to range anywhere from 2 months to 4 years, with one case reported after 9 years of treatment without any prior adverse effects (1, 14). The evidence presented here highlights the necessity to measure serum triglyceride levels prior to the initiation of treatment and throughout estrogen therapy in transgender patients. Additionally, the evidence emphasizes the

importance of withholding estrogen therapy in patients with pre-existing hypertriglyceridemia and in those who develop hypertriglyceridemia while taking estrogen therapy due to the associated increased risk of serious adverse events such as acute pancreatitis.

CONCLUSION

The prescription of hormones and the consideration of their potential side effects will continue to grow as the number of transgender people presenting to health care services continues to increase (estimated as 9.2 per 100,000) (15). The lack of current recommendations for the optimal choice of drugs, dosages, and routes has led to a general lack of understanding among most practitioners regarding treatment and management in the transgender population. Further studies are needed to adequately assess the theoretical risks of estrogen therapy in this population. The utilization of lipid panels increases in this population due to the supraphysiologic doses of sex hormones required for treatment and the dose-dependent estrogen-induced elevation in triglycerides. Due to the resulting increased risk of estrogen-induced pancreatitis and reported latency period variability in the general population, hypertriglyceridemia should be assessed prior to the initiation of treatment and throughout estrogen therapy in transgender patients.

Before initiating estrogen therapy in a transgender patient, it is imperative to illicit a thorough family history of hypertriglyceridemia and acute pancreatitis, as familial hypertriglyceridemia greatly increases the risk of estrogen-induced pancreatitis. Secondary factors contributing to hypertriglyceridemia should be evaluated and treated as their prevention may reduce the risk for acute pancreatitis. Alcohol use

should be decreased, tight glycemic control should be established, hypothyroidism should be treated, and lipid-lowering therapy with fibrates should be initiated (6, 7, 16). A multidisciplinary team is essential to treatment success in the transgender population and should include professionals familiar with both gender dysphoria and transgender hormone therapy.

Notes

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