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Case Report

Gender-Affirming Hormone Therapy With Estrogen Causing Gallstone Associated Acute Pancreatitis

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ABSTRACT

Background/Objective: Although estrogen is one of the main agents used to treat transgender women, there are few reports of acute pancreatitis (AP) of this illness in this group. The objective of this report is to describe a transgender woman who developed AP in the setting of estrogen treatment and gallstone disease.

Case Report: A 38-year-old transgender woman presented with severe abdominal pain and vomiting. Her medical history included gender dysphoria managed with gender-affirming hormone therapy comprising estradiol valerate, progesterone, and spironolactone. Initial management involved supportive care, antibiotic therapy, and endoscopic retrograde cholangiopancreatography with biliary stent placement. Imaging confirmed acute interstitial edematous pancreatitis without necrosis, guiding treatment decisions toward laparoscopic cholecystectomy. Pathological examination revealed multiple gallstones, affirming the diagnosis of AP secondary to choledocholithiasis, likely associated with estrogen use. Postprocedural recovery was uneventful, with eventual removal of the biliary stent and resolution of symptoms.

Discussion: There are only 7 reported cases in literature on estrogen-induced AP in transgender individuals undergoing gender-affirming hormone therapy. Most of these were primarily linked to hypertriglyceridemia.

Conclusion: High-dose estrogen therapy in transgender women can elevate the risk of AP through the development of gallstones, underscoring the importance of thorough patient evaluation and discussion of risks assessment prior to initiating hormone therapy.

Introduction

Per Hembree et al, "gender-dysphoric/gender-incongruent persons seek and/or are referred to endocrinologists to develop the physical characteristics of the affirmed gender".[1] For transgender women, estrogen helps with the feminization of physical appearance and can be combined with other testosterone-lowering medications. Other well-known indications for estrogen therapy are hormonal replacement therapy (HRT) in menopause, endometrial development in preparation for in vitro fertilization, and oral contraception. Gender-affirming hormone therapy (GAHT), however, necessitates higher estrogen doses (2-6 mg/d)[1] than, for example, HRT in menopause (1 mg/d).[2,3] Estrogen use in the transgender population is associated with the risk of thromboembolism and weight gain.[4] Another adverse effect of estrogen therapy, which has been documented in cisgender women, is acute pancreatitis (AP). However, there are limited reports of such entity in transgender women.[5-11]

In this case report, we describe gallstone pancreatitis after several years of treatment with estrogen in a transgender woman.

Case Report

The patient is a 38-year-old transgender Caucasian woman (assigned male at birth) who presented to the emergency department with complaints of right upper quadrant and epigastric abdominal pain as well as nonbloody nonbilious vomiting of several hours duration. Prior to admission home medications were:

Abbreviations: AP, acute pancreatitis; CBD, common bile duct; CT, computed tomography; ERCP, endoscopic retrograde cholangiopancreatography; GAHT, gender-affirming hormone therapy; HRT, hormone replacement therapy; HTG, hypertriglyceridemia; IV, intravenous; TG, triglycerides.

Informed consent: Patient has signed informed consent.

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viloxazine 400 mg daily, cetirizine 10 mg daily, escitalopram 20 mg daily, finasteride 1 mg daily, hydroxyzine 10 mg as needed, metoprolol 50 mg daily, mirtazapine 7.5 mg at night, progesterone 100 mg daily, spironolactone 100 mg twice a day, and subcutaneous injections of estradiol valerate 4 mg weekly. Her past medical history included gender dysphoria, attention deficit hyperactivity disorder, hyperlipidemia, hypertension, obesity, obstructive sleep apnea, chronic kidney disease, anxiety, and depression. She denied fever, chills, diarrhea, constipation, recent abdominal trauma, infections, previous episodes of pancreatitis, or family history of lipid metabolism disorders. The patient used alcohol 2 to 3 times a year; she had not taken alcohol recently.

Her gender dysphoria was addressed only at age of 33 years when she decided to begin GAHT. At that time, she was started on oral estradiol (initially 2 mg, then 4 mg, then 3 mg daily) and spironolactone 100 mg daily. Two years later, she was also started on progesterone 100 mg nightly. Plasma estradiol levels fluctuated, which prompted the change from oral formulation to transdermal estradiol film 0.1 mg/24 h twice weekly for more steady hormone levels. Eventually, she was switched to weekly subcutaneous injections of estradiol valerate 4 mg due to consistently below-the-goal estrogen levels as well as slow physical changes (Fig.). After 5 years of treatment with estrogen and progesterone she developed more noticeable breast growth and was happy with the therapy effects.

On physical examination, her temperature was 97.3 °F, heart rate 76 beats per minute, respiratory rate 17, blood pressure 134/86 mmHg, SpO2 99%, height 188 cm, weight 141.1 kg, body mass index 39.9 kg/m^2. There were no signs of jaundice. The abdomen was tender to palpation in the epigastrium, as well is in both left and right upper quadrants with a negative Murphy's sign. Laboratory test results presented in Table 1. Lipase >3000 U/L (reference range: 13-60), aspartate aminotransferase 455 U/L (reference range: 15-41), alanine aminotransferase 373 U/L (reference range: 7-35), total bilirubin 1.4 mg/dL (reference range: 0.3-1.2), direct bilirubin 0.71 mg/dL (reference range: 0.03-0.18) (Table 1), triglyceride (TG) level 391 mg/dL (reference range: 10-150), and white blood cell count 17.2 × 10^3/cmm (reference range: 4.3-10.8). Gallbladder ultrasound showed numerous gallstones up to 1.2 cm in the gallbladder without evidence of acute cholecystitis common bile duct (CBD) measured 6 mm. She was started on piperacillin-tazobactam, aggressive fluid resuscitation with lactated ringer intravenous infusion at 250 mL/h, ondansetron 4 mg intravenously as needed every 6 hours, acetaminophen 1 gr every 6 hours, and morphine 4 mg intravenously as needed every 3 hours. In the next several hours, magnetic resonance imaging and magnetic resonance cholangiopancreatography of the abdomen was obtained and revealed choledocholithiasis with 5 to 6 small gallstones within the CBD with the largest measuring 5 mm; CBD of 6 mm with distal tapering; diffuse pancreatic and peripancreatic edema; innumerable small gallstones in the gallbladder without gallbladder wall thickening. Endoscopic retrograde cholangiopancreatography (ERCP) showed diffuse dilation of the CBD with a diameter of 8 mm. No stones were seen. Successful extraction of a small amount of sludge was performed and a biliary stent was placed into the distal CBD.

After ERCP, the patient developed a fever of 100.1 F, and her abdominal pain and leukocytosis worsened to 24.12 × 10^3/cmm,

Highlights

- High-dose estrogen therapy in transgender women carries risk of gallstone pancreatitis.
- Risk factors of pancreatitis should be evaluated prior to initiation of such therapy.
- Patients should be aware of risks of estrogen therapy and for symptoms to watch.

Clinical Relevance

Gender-affirming therapy is associated with use of high doses of estrogen. This can increase the risk of acute gallstone pancreatitis. Clinicians should be familiar with this adverse effect and inform their patients, so they can make informed decision on whether or not to proceed with the therapy.

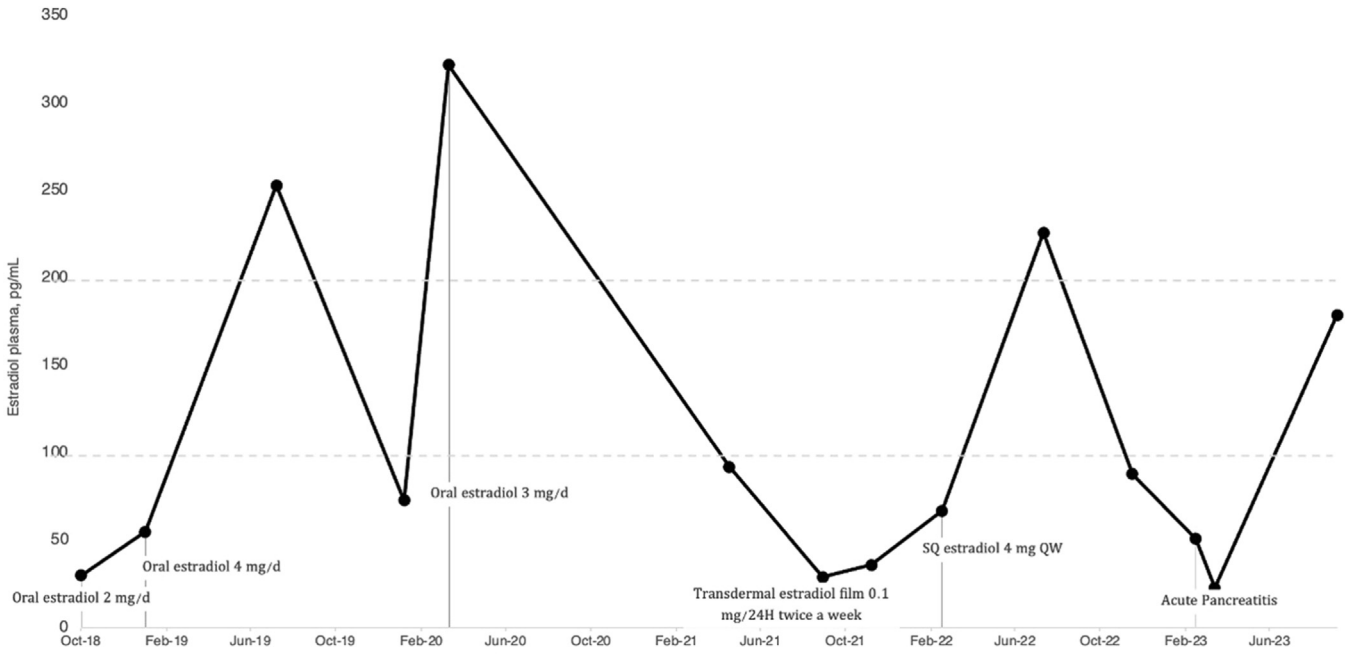

Fig. Estradiol plasma concentrations and estrogen therapy doses. *QW* = every week; *SQ* = subcutaneous.

Table 1
Laboratory Results on Presentation

Laboratory test	Result	Reference range
Creatinine	1.24	0.9-1.3 mg/dL
CO2	22	22-32 mmol/L
Anion gap	15	10-20 mmol/L
Glucose	(H) 218	70-99 mg/dL
Calcium	9.5	8.6-10.3 mg/dL
Albumin	4.6	3.5-4.8 g/dL
Total bilirubin	(H) 1.4	0.3-1.2 mg/dL
Direct bilirubin	(H) 0.71	0.03-0.18 mg/dL
Alkaline phosphatase	82	40-129 U/L
AST	(H) 455	15-41 U/L
ALT	(H) 373	7-35 U/L
Lipase	(H)>3000	13-60 U/L
Cholesterol	(H) 206	0-200 mg/dL
Triglyceride	(H) 391	10-150 mg/dL
CRP	(H) 298.9	>100 mg/L—serious processes/bacterial infection
WBC	(H) 12.70	4.3-10.8 10^3/cmm

Abbreviations: CRP = C-reactive protein; ALT = alanine aminotransferase; AST = aspartate aminotransferase; WBC = white blood cell count.

computed tomography of the abdomen was performed, which redemonstrated sequela of acute interstitial edematous pancreatitis, including diffuse pancreatic edema with surrounding fat stranding, but no definite pancreatic necrosis, focal fluid collection, abscess, or free air were seen. She gradually improved on continuous intravenous lactated ringer infusion, ondansetron, acetaminophen, and morphine and underwent laparoscopic cholecystectomy a few days later. Her pain resolved and she was tolerating oral intake. She was discharged after being hospitalized for a total of 6 days. Pathology report of the gallbladder revealed multiple yellow-white spherical gallstones ranging in size from 4 mm to 9 mm. Eight weeks later, she underwent repeat ERCP for the stent removal, which showed dilation of the CBD with a diameter of 8 mm. The stent was retrieved and extraction of a small amount of sludge and 2 stones with complete clearance of the duct was achieved.

The patient continues to take progesterone 100 mg daily, spironolactone 100 mg twice a day, and subcutaneous injections of estradiol valerate 4 mg weekly and states that she is happy with the transition she is making.

Discussion

We presented a transgender woman who developed severe acute gallstone pancreatitis in the setting of estrogen treatment. AP is an acute inflammation of the pancreas with incidence 4.8 to 24.2 per 1 000 000.[12] Diagnosis is made when 2 out of 3 criteria are present: elevated lipase 3 times higher the upper limit of normal, characteristic epigastric pain, or computed tomography evidence of AP.[13] The most common causes of AP are gallstones, alcohol use, hypertriglyceridemia (HTG), and medications use including estrogen treatment. Gallstone-induce pancreatitis is caused by gallstone CBD obstruction causing increasing duct pressure and activation of digestive enzymes. Alcohol presumably might cause direct sensitization of acinar cells causing cholecystokinin stimulation. Also, inability to inhibit trypsin activity can predispose to alcoholic pancreatitis.[14] HTG is the third most common cause of AP, accounting for 1% to 14% of all AP cases,[15] and serum concentrations of TG exceeding 1000 mg/dL have the potential to precipitate AP.[16] Estrogen causes decrease of lipoprotein lipase activity which leads to elevation of very-low density lipoproteins levels, which in turn increase concentration of chylomicrons and TG. A high concentration of chylomicrons and free fatty acids is assumed to increase plasma viscosity, which eventually leads to AP.[17] Another cause of AP, obesity, can promote high cholesterol turnover causing supersaturation of the bile, which might cause precipitation and gallstone formation.[18] Other etiologies of AP include pancreatic trauma, hypercalcemia, infections, genetic predisposition, and exposure to toxins. In the absence of other causes of AP, we assume that in our patient high-dose estrogen therapy could have contributed to the development of the gallstones and subsequently lead to AP.

To date, there are only 7 cases of estrogen-induced AP reported in transgender women and all of them but 1 were driven by HTG[5,7-11] (Table 2). In all 6 cases, authors linked high-dose oral estrogen (4-8 mg daily) and HTG (20 730 - >7000 mg/dL), which was an assumed culprit for AP. Tirthani et al did not exclude the possibility of transient obstruction of bile ducts with gallstones but the more obvious cause of AP was HTG in addition to euglycemic diabetic ketoacidosis in the settings of sodium-glucose cotransporter-2 inhibitors use.[11] No other causes of HTG or AP were identified in any of these cases.

Only 1 case of gallstone pancreatitis without hypertriglyceridemia in a transgender woman has been reported so far.[6] Similarly to that case, our patient had only mild elevation of TG, but she had cholelithiasis with sludge and choledocholithiasis. Gallstones are the most common cause of AP in the general population, responsible for 40% to 70% of cases. There is an association between estrogen use and gallstone development. One of the most important risk factors for gallstone formation is female gender, and sex hormones presumably are responsible for that. Estrogens can increase liver secretion of cholesterol causing cholesterol supersaturation of bile, which in turn might lead to gallstone formation and increased risk of AP. HRT has been described to be linked with gallstone disease.[19] Reportedly, this effect is likely dose-dependent, and only higher doses of estrogens, similar to those used in GAHT, are prone to cause gallstone development.[20] In our case, the yellow color of the gallstones in the pathology report is suggestive of the cholesterol composition of the stones, which can be associated with high-dose estrogen therapy.

None of the previous case reports mentioned the estrogen plasma concentrations, thus it is unknown whether they were higher than the GAHT target of 100 to 200 pg/mL.[1] It is undetermined whether high estrogen plasma concentrations could contribute to AP rather than high doses of estrogen therapy alone. In our case, the most recent serum estrogen level before AP was 51 pg/mL, though throughout 5 years of GAHT fluctuated from 23 to 322 pg/mL (Fig. 1).

Table 2
Case Reports of Acute Pancreatitis in Transgender Women

Author, y	Country	Age, y	TG level, mg/dL	Gallstones	BMI, kg/m2	Alcohol use	Estrogen therapy formulation and dose	Estrogen therapy duration, mo/y	Continuation of estrogen therapy
Perego et al, 2004	Italy	37	5174	No	No data	No	Conjugated estrogens 0.625 mg, ethinyl estradiol 0.035 mg daily, route not reported	3 mo	Discontinued
Goodwin et al, 2018	US	51	2073	No	31	No	PO estradiol, 4 mg/d	10 y	No data
Shipley et al, 2020	US	31	>7000	No	No data	5-6 drinks/wk, occasional binge-drinking	PO estrogen, dose not reported	2 mo	Discontinued
Hashmi et al, 2021	UK	52	6377*	No	No data	No data	PO estradiol, 8 mg/d	5 y	Discontinued
Chaudhry et al, 2021	US	51	>5000	No	29.8	No	PO estradiol, 4 mg/d	No data	No data
Tirthani et al, 2021	US	34	2142	Yes	31.3	4 drinks/wk	PO estradiol, 6 mg/d	No data	Discontinued
Freier et al, 2021	US	24	159	Yes	35.7	3-4 drinks/wk	PO estradiol, 4 mg/d	No data	Continued
Our case, 2024	US	38	391	Yes	39.9	3-4 drinks/y	SQ estrogen, 4 mg/wk	5 y	Continued

Abbreviations: BMI = body mass index; PO = per os (oral); SQ = subcutaneous; TG = triglycerides.
* Reported as 72 mmol/L, conversion from mmol/L to mg/dL was done by multiplying by 88.75.

In conclusion, high-dose estrogen therapy in transgender women increases the risk of AP secondary to gallstones. While recognizing that transgender medicine is still developing, physicians should be familiar with the possible adverse effects of high-dose estrogen therapy and should inform patients about the potential risks of AP. Prior to initiation of such therapy, personal and family history of HTG and AP, alcohol use, and uncontrolled diabetes should be evaluated. Further studies are needed to assess the association between estrogen use in the scope of GAHT and the risks of AP.

Disclosure

The authors have no conflicts of interest to disclose.

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