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REVIEW

A Case Study and Review of Pancreatitis in the AIDS Population

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Abstract This case study considers a 55-year-old African American woman with the acquired immunodeficiency syndrome (AIDS) who presented with epigastric abdominal pain for 1 week. She was found to have pancreatitis on computed tomography scanning. Unique to this case are the numerous possible etiologies of her pancreatitis. Thus, this case study systematically reviews the different etiologies of pancreatitis in the AIDS population compared to the general population. Furthermore it discusses the management and treatment of pancreatitis in AIDS.

Keywords Acquired immunodeficiency syndrome · Highly active antiretroviral therapy · Pancreatitis · Human immunodeficiency virus · Hypertriglyceridemia

The Case

A 55-year-old African American woman presented to the Emergency Department at The Mount Sinai Medical Center with epigastric abdominal pain for 1 week. The pain was sharp, nonradiating, exacerbated by eating, and associated with nausea and vomiting. Her past medical history included gallstone pancreatitis with resultant cholecystectomy, AIDS with a CD4 count of 182, familial hypertriglyceridemia previously controlled with fenofibrate, and insulin dependent diabetes mellitus. Her medications included atazanavir, abacavir, lamivudine, trimethoprim-sulfamethoxazole, fenofibrate, human lantus insulin, human aspart insulin, gabapentin, estradiol transdermal, and progesterone micronized. On physical examination the patient appeared uncomfortable with dry mucus membranes. Abdominal exam revealed epigastric tenderness without palpable masses or peritoneal signs. Vital signs and laboratory values as per Ranson and APACHE II (Acute Physiology and Chronic Health Evaluation II) are displayed in Tables 1 and 2, respectively.

According to APACHE II and Ranson's criteria the patient did not meet the definition of severe pancreatitis (APACHE II score <8, Ranson score = 2). Other pertinent laboratory values revealed a lipase of 441 U/l, an amylase of 61 U/l, and a triglyceride level of 1,542 mg/dl. A contrast-enhanced CT scan of the abdomen and pelvis demonstrated significant inflammatory stranding and a fluid collection close to the head of the pancreas without discrete necrosis (Fig. 1a). Prior imaging (performed 1 year earlier after resolution of an episode of pancreatitis) is shown for comparison (Fig. 1b).

The patient was diagnosed with acute interstitial pancreatitis with fluid collections in the setting of hypertriglyceridemia. Her HAART regimen, trimethoprim/sulfamethoxazole, and estrogen/progesterone therapy were held. She was made NPO and received total parenteral nutrition (TPN). She received intravenous narcotics for pain control. Her insulin regimen was adjusted to optimize her blood glucose control and she was continued on

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Table 1 Ranson's criteria at admission and at 48 h

Ranson's criteria	Admission	48 h
Age >55	55	55
Leukocytes $>16 \times 10^9$	4.6	4.4
Blood glucose >200	240	245
Serum lactate dehydrogenase >350	592	359
Serum aspartate aminotransferase >250 IU/l	38	39
Hematocrit decrease >10%	NA	Absent
Blood urea nitrogen increase >5 mg/dl	NA	Absent
Serum calcium <8 mg/dl	NA	Absent
Arterial PaO_2 <60 mmHg	NA	Absent
Base deficit >4 mEq/l	NA	Absent
Fluid sequestration >6 l	NA	Absent

NA not applicable

antilipid therapy. Her abdominal pain resolved, and the triglyceride level normalized. Serial CT imaging throughout her 3 week hospital stay displayed a parallel improvement with a progressive decrease in inflammation. She was discharged home with TPN and scheduled for a follow-up CT scan to evaluate the fluid collection within her pancreas.

Discussion of Diagnosis

Acute pancreatitis is an inflammatory condition of the pancreas caused by premature activation of zymogens that are usually activated in the duodenum though the pathophysiology is not clearly elucidated. Pancreatitis may be of the interstitial type or the necrotizing/hemorrhagic type. The two are differentiated by the latter having parenchymal destruction with peripancreatic fat necrosis. In pancreatitis caused by hyperlipidemia, it has been proposed that free fatty acids are released from serum triglycerides by pancreatic lipase in toxic concentrations and thus cause premature activation of zymogens [1]. Serum triglyceride concentrations greater than 1,000 mg/dl predispose patients to acute pancreatitis.

Clinically, patients present with upper abdominal pain that often radiates to the back and may be relieved by sitting forward. The pain is usually accompanied by nausea

Table 2 APACHE II scores at admission and 48 h

Criteria	Admission	48 h
Rectal temperature, °C	36.5	37.2
Mean blood pressure, mmHg	92	90
Heart rate, beats/min	99	86
Respiratory rate, breaths/min	16	16
Oxygenation FIO_2 (kPa)	Oxygen saturation 99% on 21% FIO_2	Oxygen saturation 99% on 21% FIO_2
Arterial pH	7.33	7.35
Serum sodium mmol/l	139	138
Serum potassium mmol/l	4.9	4.7
Serum creatinine (μmol/l)	190	70
Packed cell volume %	NA	NA
White blood cell count $\times 10^9$	4.6	4.4

NA not available

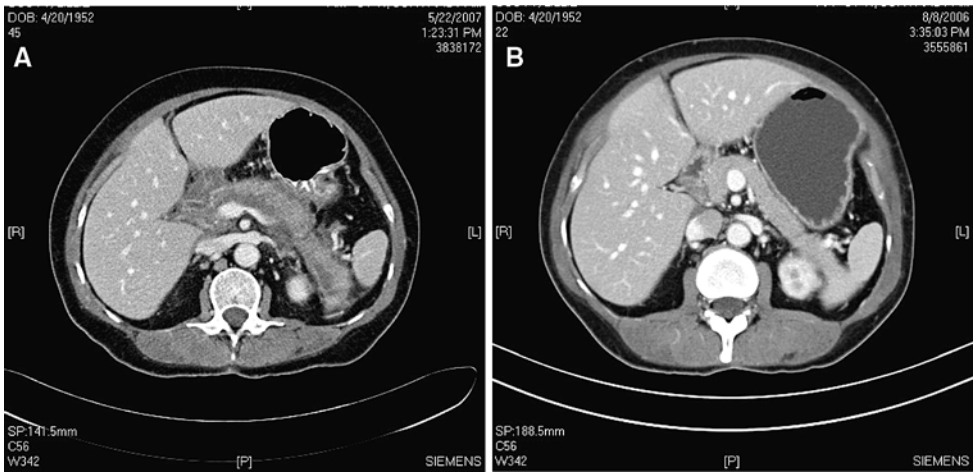

Fig. 1 (**a**) CT of the abdomen showing a heterogeneous pancreas with a fluid collection. There was no enlargement of the hepatic, common bile, or pancreatic duct. (**b**) Previous CT showing a homogenous pancreas with mild stranding in the tail of the pancreas

and vomiting. Physical examination can range from mild to severe abdominal tenderness to palpation, with or without abdominal distention, guarding, and Cullen's and Grey-Turner signs (ecchymotic discoloration in the periumbilical region and flank, respectively).

The diagnosis of acute pancreatitis requires one of the following criteria: serum lipase or amylase greater than three times normal, findings on ultrasound or CT, or surgical confirmation [2]. The sensitivity of serum lipase ranges from 85% to 100% [3]. The amylase level is falsely low in the setting of hyperlipidemia. In the case discussed here, the diagnosis was confirmed by CT imaging as the patient's lipase and amylase values were less than three times the normal value and thus not diagnostic.

Pancreatitis is a relatively common cause of morbidity in the HIV population. Retrospective studies have shown that acute pancreatitis occurs 35–800 times more frequently in this population [4]. The most common cause of acute pancreatitis in the HIV population are medications. Guo et al. studied 4,972 patients with HIV who were on at least one antiretroviral drug. His group found that 159 patients (3.2%) developed pancreatitis [5]. In the general population, the most common etiologies of pancreatitis include biliary tract disease, alcohol, and hypertriglyceridemia, in addition to medications. All of these factors must also be considered in the evaluation of HIV positive patients with pancreatitis.

In the evaluation of patients with pancreatitis a comprehensive medical and social history should be performed including medication use and alcohol intake. Ultrasonography should then be performed to evaluate for gallstones. If the etiology is still unclear, lipid levels should be drawn. Abdominal CT or magnetic resonance imaging can also be performed to evaluate for anatomical abnormalities.

Differential Diagnosis in HIV Population

In the case discussed here, the patient was diagnosed with pancreatitis secondary to hypertriglyceridemia in the setting of HAART (atazanavir, abacavir, and lamivudine), familial hypertriglyceridemia, estrogen therapy, and sulfonamide medication. In this case, the etiology of pancreatitis may have been mulitfactorial. Our case provides an opportunity to review of the different causes of pancreatitis in the HIV-infected population.

Protease Inhibitor Induced Hypertriglyceridemia

It is documented in the literature that patients with HIV are predisposed to dyslipidemia. Increased triglyceride and decreased cholesterol levels [6] are thought to be associated with increased circulating levels of cytokine interferon alpha [7]. Protease inhibitor (PI)-based antiretroviral medications are associated with increases in LDL and triglycerides and decreases in HDL. These changes usually take place 2–3 months after initiation of therapy. Triglycerides may increase to greater than 1,000 mg/dl and therefore increase the risk for pancreatitis and atherosclerosis [7]. In an analysis of 23,000 HIV-infected patients in Data Collection on Adverse Events of anti-HIV Drugs (D:A:D), investigators demonstrated that the risk of hypertriglyceridemia was greatest with PIs, especially ritonavir [8]. The pathophysiology of PI-induced dyslipidemia is poorly understood. One proposed mechanism is that PIs bind to a protein that inhibits adipocyte apoptosis. Thus, there is increased apoptosis of adipocytes, decreased lipid storage, and lipid release into the blood stream [7].

Our patient was receiving the protease inhibitor atazanavir without ritonivir. Although PIs as a class seem to predispose patients to dyslipidemias, atazanavir itself has not been previously reported to be associated with hypertriglyceridemia [9]. Nucleoside reverse transcriptase inhibitors (NRTIs) are associated with fewer lipid changes than PIs. However, stavudine has been associated with elevated triglyceride levels [10]. In general, non-nucleosidase reverse transcriptase inhibitors (NNRTIs) are not associated with dyslipidemia [11].

NRTI Induced Lactic Acidosis/Mitochondrial Injury

NRTIs such as zidovudine (AZT), stavudine (d4T), and didanosine (ddI) can often cause pancreatitis in the setting of lactic acidosis [12]. In a study from Johns Hopkins, 2,613 patients were followed longitudinally while on a regimen that included d4T, ddI, or AZT. Thirty-three developed pancreatitis. The reported relative risk was 1.0 for ddI (the reference), 1.4 for d4T, 2.08 for ddI + d4T, and 0.18 for AZT. A CD4 count below 200×10^6 cells/l and a history of pancreatitis (both of which our patient had) were found to be associated with an increased relative risk of pancreatitis as well [13]. There have also been three case reports of pancreatitis from tenofovir (also an NRTI) and low dose didanosine regimens. These case reports came after cases of full dose didanosine and tenofovir were implicated in cases of pancreatitis [14]. The pathophysiology of pancreatitis related to NRTIs is thought to be due to mitochondrial toxicity which can occur via nucleoside analog mediated inhibition of DNA polymerase gamma and subsequent depletion of mitochondrial DNA [12]. In our case, the patient was on two NRTIs (abacavir and lamivudine) that are rarely if ever implicated with pancreatitis. Furthermore, her lactate level from arterial blood

was only 0.7 mM. Thus, pancreatitis from NRTI related mitochondrial toxicity in unlikely.

Opportunistic Infections

Patients with HIV are prone to infection with declining CD4 counts. Cytomegalovirus (CMV) has been reported in the literature to cause pancreatitis [15]. However, gastrointestinal CMV usually presents with esophagitis or colitis. The CD4 count is usually less than 50/mm^3. Less common causes include mycobacterium avium complex, tuberculosis, cryptosporidium, toxoplasmosis, and cryptococcus [15].

Familial Dyslipidemia

Familial dyslipidemia may result in hypertriglyceridemia and pancreatitis. From the literature, the most common dyslipidemias presenting with pancreatitis are type 1 (35%), type II (15%), and type V (30–40%). Our patient stated that she was diagnosed with hypertriglyceridemia many years ago and that her mother also had elevated lipids. Her triglycerides had been controlled with daily fenofibrate prior to presentation. A review of her lipid profiles from the 3 years prior to presentation, including the time period of her first episode of gallstone pancreatitis, showed triglyceride levels consistently below 500.

Drugs

Drugs that have been associated with pancreatitis include alpha methyl dopa, azathioprine, cimetidine, estrogens, furosemide, INH, metronidazole, pentamidine, rifampin, salicylates, sulfasalazine, sulfonamides, tetracycline, and valproic acid [2]. Our patient was receiving two of these medications—estrogen injections once a week for menopausal symptoms and trimethoprim/sulfamethoxazole for prophylaxis against opportunistic infections.

Biliary Tract Disease

Gallstones are the leading cause of pancreatitis in women. Given her history of gallstone pancreatitis and cholecystectomy, we considered choledocholithiasis as a possible etiology of pancreatitis. However, imaging did not demonstrate common bile duct dilation. For these reasons, the biliary tract seemed an unlikely cause of pancreatitis here.

Other Causes

In our workup of this patient, we ruled out other potential contributing causes such as alcohol, hypercalcemia, abdominal trauma, and anatomical variations.

Treatment and Management

Treatment of interstitial pancreatitis is different from necrotizing pancreatitis. With interstitial pancreatitis the treating physician should restrict oral intake, administer intravenous fluids, and prescribe medications for pain relief. Inciting factors such as medications should be minimized. For all patients a Ranson or APACHE II score should be calculated. This allows the physician to predict the presence of pancreatic necrosis, which presents a higher risk of morbidity and mortality. A Ranson score of 3 or more or an APACHE II of 8 or more is suggestive of pancreatic necrosis and is an indication for abdominal CT imaging to evaluate for necrosis. Patients with acute pancreatitis who do not improve with conservative management should also undergo cross-sectional imaging [2].

Management of acute necrotizing pancreatitis is similar but entails more intense monitoring as the morbidity and mortality is much higher than for interstitial pancreatitis. Patient's should be in a closely monitored setting (i.e. ICU setting) as they are at an increased risk of acute respiratory distress syndrome, pleural effusions, myocardial depression, renal failure, and shock. Surgical debridement may be necessary. Patients with necrotizing pancreatitis may be given imipenem-cilastatin as pancreatic infection occurs through bacterial translocation from the colon. As with interstitial pancreatitis, oral intake should be restricted and aggressive fluid resuscitation performed [2].

In HIV patients, treatment-related hypertriglyceridemia, mitochondrial toxicity from NRTI, and opportunistic infections should be considered as potential etiologies of pancreatitis. It is reasonable to hold antiretroviral medications pending evaluation and resolution.

In patients with PI-induced hypertriglyceridemia, the effect of changing from a PI-based treatment to a PI-sparing treatment regimen has been evaluated. In such regimens the PI is replaced with nevirapine (NNRTI), efavirenz (NNRTI), or abacavir (NRTI). This is usually successful in patients who already have long-lasting viral suppression. In patients who develop NRTI-related pancreatitis secondary mitochondrial toxicity, the drugs should be stopped as well. Once the episode resolves, a new (possibly NRTI-sparing) HAART regimen should be considered. The patient's HIV doctor should be involved in all decisions related to HAART.

Patients on antiretroviral therapy should have a lipid profile checked every 3–4 months after initiating therapy, and at least annually if lipids are stable. In addition, a hypolipidemic diet, exercise, smoking cessation, weight loss, and pharmacotherapy can help lower triglyceride levels and decrease the risk of pancreatitis. For triglyceride levels greater than 500 mg/dl, therapy with gemfibrozil or fenofibrate is considered standard of care if antiretroviral regimen cannot be safely modified [1, 3, 6].

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