

CASE REPORT

Azathioprine Induced Pancreatitis in a Patient with Co-Existing Autoimmune Pancreatitis and Hepatitis

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ABSTRACT

Context Azathioprine induced pancreatitis usually runs a benign self limited course with rapid disappearance of signs and symptoms upon withdrawal of the drug. Azathioprine is used in treating relapses in patients with autoimmune pancreatitis and maintenance of remission in autoimmune hepatitis. Acute pancreatitis complicated by symptomatic pseudocysts requiring drainage is not usually associated with drug induced pancreatitis. The risk of azathioprine use in patients with underlying disease of pancreas including autoimmune pancreatitis is unclear. **Case report** We report here a case of an African American patient with co-existing autoimmune pancreatitis and autoimmune hepatitis who developed azathioprine induced acute pancreatitis complicated by a large symptomatic pseudocyst compressing the duodenum requiring a cystoduodenostomy. **Conclusions** Future studies to investigate the risk of azathioprine induced pancreatitis in the presence of underlying disease of the pancreas including autoimmune pancreatitis are required to further understand the safety of azathioprine in this subgroup of patients.

INTRODUCTION

Azathioprine is implicated as a definite cause of drug induced pancreatitis [1]. Azathioprine is used in a number of diseases including inflammatory bowel disease (IBD), post transplantation, vasculitis, autoimmune hepatitis; however acute pancreatitis is rarely reported except in IBD [2]. Patients who develop azathioprine associated pancreatitis usually have underlying other factors co-existing/responsible for acute pancreatitis [3, 4].

Azathioprine induced pancreatitis is generally mild and rapidly responds to the withdrawal of the drug except in patients following transplantation where a fatal outcome is reported [5, 6]. The incidence of azathioprine induced pancreatitis is more frequent in patients with underlying IBD than other conditions where azathioprine is used. The risk of acute pancreatitis in azathioprine exposed patients is reported to be around 1.4-1.6% [7, 8]. Population based studies report that patients treated with azathioprine are at eight-fold increased risk to develop acute pancreatitis [9].

Autoimmune pancreatitis is a recently described systemic fibro-inflammatory disease affecting the pancreas along with a variety of other organs including the bile duct, salivary glands, and the retroperitoneum [10, 11, 12]. It is characterized histologically by an IgG4-positive lymphoplasmacytic infiltrate [12]. It classically presents with jaundice associated with a pancreatic mass, pancreatic and/or biliary duct strictures and elevation of serum gamma globulin (IgG4), and it responds favorably to steroids [13].

Autoimmune pancreatitis is exceedingly rare in African Americans and has been reported thus far in isolated case reports [14, 15]. Co-existing autoimmune pancreatitis and autoimmune hepatitis or primary sclerosing cholangitis has been reported in literature, given the underlying autoimmune predisposition of this group of patients [16]. Azathioprine has an established role in maintaining remission in autoimmune hepatitis [17] because relapse is much more common in autoimmune hepatitis. However, there is insufficient evidence to support prolonged immunosuppression in patients with autoimmune pancreatitis [18]. Although a recent small study of 28 patients reported that azathioprine was effective in the management of post-treatment relapse; the optimal treatment of relapse is still unclear [19]. The safety of azathioprine in this subgroup of patients is also unclear.

We report here a case of an African American patient with co-existing autoimmune pancreatitis and autoimmune hepatitis who was started on azathioprine for maintenance immunosuppression for autoimmune hepatitis and autoimmune pancreatitis, developed acute

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azathioprine induced pancreatitis complicated by a large symptomatic pseudocyst compressing the duodenum requiring a cystoduodenostomy.

CASE REPORT

The patient was a 51-year-old African American male who was in his usual state of health. All his symptoms started in October 2002 when he had presented with diffuse non-specific abdominal pain. At that time, he underwent extensive laboratory and imaging workup which was unrevealing. His abdominal pain persisted and no clear etiology was evident. In September 2003, while donating blood, he was found to have elevated liver enzymes. With his abdominal pain and elevated liver enzymes, he was referred to our center for further workup.

Biochemical evaluation revealed abnormal liver function tests (aspartate aminotransferase (AST) 169 IU/L, reference range: 15-40 IU/L; alanine aminotransferase (ALT) 226 IU/L, reference range: 15-40 IU/L; alkaline phosphatase (ALP) 689 IU/L, reference range: 20-140 IU/L; total bilirubin 1.6 mg/dL, reference range: 0.6-1.2 mg/dL). Iron panel, rheumatoid factor, anti-nuclear antibody, anti-mitochondrial antibody and liver panel for hepatitis viruses were negative. Anti-smooth muscle antibodies were positive (1:20). CA 19-9 was elevated at 43 U/mL (reference range: 0-37 U/mL). He was also found to have elevated IgG of 1,985 mg/dL (reference range: 717-1,411 mg/dL) and IgG4 of 253 mg/dL (reference range: 8-140 mg/dL).

Computerized tomography (CT) of the abdomen revealed mild intrahepatic and extrahepatic ductal dilation, prominent pancreatic head, and multiple small hepatic lesions. An endoscopic retrograde cholangiopancreatography (ERCP) was done which revealed a diffuse stricture in the intrahepatic duct, and a small pancreatic duct without strictures with a narrow bifurcation at the level of both the common hepatic ducts. Brushings were negative for malignancy. Endoscopic ultrasound (EUS) showed a hypoechoic enlarged pancreatic head and fine needle aspiration (FNA) was negative for malignancy. With the presence of the pancreatic head mass, an elevated IgG, particularly IgG4, the diagnosis of autoimmune pancreatitis was provisionally made.

Elevated liver function tests and positive smooth muscle antibodies were suspicious for possible co-existing autoimmune hepatitis vs. IgG4 associated cholangitis. Also his ERCP had revealed diffuse intrahepatic ductal stricture. Intraductal biopsy specimens did not show any evidence of IgG4 associated cholangitis, while his liver biopsy did show chronic hepatitis with mild activity grade II, periportal fibrosis with focal bridging fibrosis stage II consistent with the diagnosis of autoimmune hepatitis. He was then started on oral prednisone 50 mg/day with an 8-week tapering course.

Most of the symptoms of the patient, particularly the right upper quadrant abdominal pain, subsided after a

few months. His pancreatic head mass also disappeared. His liver enzymes were trending down by May 2004 (AST: 72 IU/L; ALT: 54 IU/L; ALP: 65 IU/L; total bilirubin: 0.8 mg/dL). The patient was continued on maintenance steroids. During a routine clinical follow-up visit in the fall of 2005 for abdominal pain, imaging in the form of abdominal CT was done which showed a lesion in the head of the pancreas measuring 2.1x2.1 cm, a slight increase in the size of an uncinete process lesion measuring 3.0x2.7 cm which was highly suggestive of an inflammatory process. He had a prior CT imaging six months before which showed few cysts in the pancreas; all were small and asymptomatic. Because of the slight increase in the size of the uncinete process cyst, EUS was performed with FNA, which revealed no malignant cells. Azathioprine at a dose of 2 mg/kg was discussed and started with steroids for autoimmune pancreatitis induced pseudocyst and also for maintaining remission in autoimmune hepatitis.

Two weeks after the initiation of azathioprine, he was admitted with severe abdominal pain, nausea and vomiting and elevated amylase and lipase. The pancreatic pseudocyst of the head of the pancreas was increased in size (4.0x3.9 cm), the remainder of the hypodense lesions of the pancreas were also slightly larger in size. A diagnosis of azathioprine-induced pancreatitis was made, as exploration for other causes of worsening was negative. He had a EUS evaluation to rule out other causes including intraductal papillary mucinous neoplasm. He had no history of alcohol abuse or cigarette smoking. There was no evidence of choledocholithiasis and evaluation of the medication list for any cause of pancreatitis other than azathioprine was negative. Azathioprine was stopped and mycophenolate mofetil was started for autoimmune hepatitis and autoimmune pancreatitis. Repeat CT after 4 weeks for persistent abdominal pain, nausea and vomiting showed extrinsic compression of the duodenum by the pseudocyst (Figure 1). ERCP with cyst duodenostomy was performed at that time with subsequent improvement of symptoms and biochemical improvement.

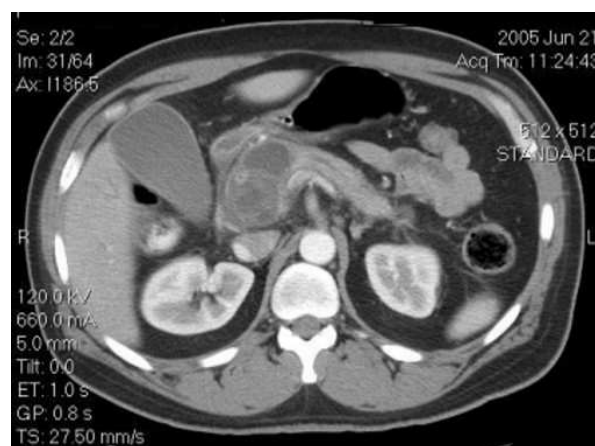


Figure 1. CT abdomen showing pseudocyst in the head of the pancreas compressing the common bile duct and duodenum.

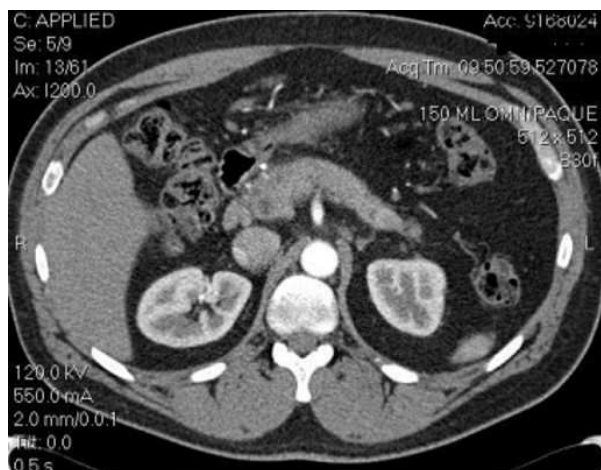


Figure 2. Complete resolution of the pseudocyst post procedure.

A follow-up CT six months later showed a significant decrease in the size of the pseudocyst (Figure 2). He was pain free and his liver function test at this time has returned to normal. The patient was instructed to continue taking ursodeoxycolic acid, prednisone and mycophenolate mofetil.

DISCUSSION

Azathioprine, implicated as a definite cause of drug induced pancreatitis is particularly seen in patients with underlying IBD and following transplantation [1, 2]. Azathioprine induced pancreatitis is generally mild and is believed to be idiosyncratic and dose-independent [20]. It usually has a benign course starts after a latent period of about 3-6 weeks after drug exposure and all signs and symptoms rapidly respond over a period of 1-11 days upon withdrawal of the drug [21]. The development of azathioprine-induced pancreatitis is usually considered a contraindication to future use [22]. The risk of acute pancreatitis in azathioprine exposed patients is reported to be around 1.4-1.6% [7, 8] and population based studies report that patients treated with azathioprine are at eight-fold increased risk to develop acute pancreatitis [9]. Studies in animal models suggest that azathioprine causes biochemical and histological evidence of acute pancreatitis [23] and aggravates acinar cell necrosis [24]. Some authors suspect that azathioprine is a co-factor in causing pancreatitis as most patients have additional possible factors for the disease [3, 4]. Given the mild presentation in most patients with azathioprine pancreatitis in the literature, it was really surprising that our patient had a complicated course requiring endoscopic intervention.

Autoimmune pancreatitis is probably one aspect of a multisystem disease characterized by involvement of affected tissues by an IgG4-positive plasma cell infiltrate [10, 11, 12]. It has not been well described in African Americans and has been reported thus far in isolated case reports [14, 15] (personal communication, Dr. Suresh Chari). Our patient was an African American, which is exceedingly rare. The disease process in autoimmune pancreatitis is reported to either

spontaneously improve [25, 26, 27] or respond dramatically to steroids [13, 18, 28]. In fact, a response to steroids is a component of the diagnostic algorithm for autoimmune pancreatitis [13, 26]. Nevertheless, the dose and duration of steroid therapy, and long term outcome following treatment is not exactly clear. Several studies report a relapse rate of 19-55% following treatment with steroids [13, 18, 29, 30]. However, the treatment of relapse is unclear. There is insufficient evidence to subject these patients to prolonged immunosuppression [18]. Although a recent small study of 28 patients reported that azathioprine was effective in the management of post-treatment relapse; the controversy still persists [19]. Our patient also had pseudocysts while on treatment with steroids. Autoimmune pancreatitis in general is not usually associated with pseudocysts [31, 32]. Data show that pseudocyst development in autoimmune pancreatitis may occur after prolonged disease activity. Pseudocysts in autoimmune pancreatitis are indicative of active inflammation and may respond well to steroids, unlike pseudocysts not associated with autoimmune pancreatitis [31]. Our patient had pseudocysts because of autoimmune pancreatitis, which continued to persist even with steroid use. The switch to azathioprine in a patient with a small pseudocyst which could have been an indicator of disease activity or pancreatic inflammation may have contributed to more severe pancreatitis.

Autoimmune pancreatitis and autoimmune hepatitis or primary sclerosing cholangitis co-existence has been reported in literature. However whether it is an incidental association or has a clear relevance is not known [16]. Azathioprine has an established role in maintaining remission in autoimmune hepatitis [17]. Relapse is much more common in autoimmune hepatitis and azathioprine is clearly beneficial in these patients. Mycophenolate mofetil can also be used as second-line agent for treating autoimmune hepatitis [33, 34]. We used azathioprine in maintaining remission in patients with autoimmune hepatitis and autoimmune pancreatitis. Two weeks later he developed azathioprine-induced pancreatitis complicated by a pseudocyst which required stopping azathioprine, starting him on mycophenolate mofetil and draining the cyst endoscopically.

The safety of azathioprine in patients with autoimmune pancreatitis is unclear. In a recent small study of 28 patients with autoimmune pancreatitis, 7 patients were maintained on remission with azathioprine monotherapy. No adverse events were reported in the study [23]. Although the preliminary results show that azathioprine was safe and effective in the management of post-treatment relapse; the safety of azathioprine is still unclear as the study population was small [23]. The safety of azathioprine in patients who have other underlying diseases of the pancreas is also not studied yet. In patients with autoimmune hepatitis, azathioprine-induced pancreatitis is reported very rarely [17, 35, 36].

The co-existence of IgG4-associated autoimmune hepatitis and autoimmune pancreatitis has been reported. In a series from Japan, more than 3% of patients with autoimmune hepatitis had IgG4-positive plasma cell deposition in the liver [37]. However, we did not see any IgG4-plasma cell deposition in the liver of our patient. Thus the co-existence of autoimmune hepatitis and autoimmune pancreatitis may be an incidental association.

The development of pancreatitis requiring endoscopic intervention in our patient may have been contributed by the presence of underlying autoimmune pancreatitis with a small pseudocyst to begin with. We hypothesize that azathioprine in the presence of a pre-existing cofactor is more prone to cause pancreatitis and patients with autoimmune pancreatitis have this predisposition with altered pancreatic parenchyma. Thus the second hit in the form of azathioprine could have triggered a severe pancreatitis. The temporal relationship between the drug and the development of symptoms with improvement upon withdrawal of the drug supports azathioprine as the cause for pancreatitis. Further studies are needed to study further our hypothesis.

CONCLUSIONS

Our case report illustrates three important issues. Firstly, the occurrence of autoimmune pancreatitis in the African American population. Secondly, the ability of azathioprine induced pancreatitis to cause symptomatic pseudocyst compressing the duodenum and requiring cystoduodenostomy. Thirdly, our hypothesis that azathioprine induced complications may be more common in patients with underlying disorder of the pancreas like autoimmune pancreatitis, which questions the use of azathioprine in the long term maintenance management of patients with autoimmune pancreatitis particularly since the chances of relapse are relatively low and their treatment is not proven.

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