TWO EPISODES OF ACUTE PANCREATITIS TRIGGERED BY CONSECUTIVE ADMINISTRATION OF 5-AMINOSALICYLIC ACID AND AZATHIOPRINE THERAPY FOR CROHN’S DISEASE

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ABSTRACT
Acute pancreatitis is a rare but potentially fatal adverse effect of both 5-Aminosalicylic Acid and Azathioprine. Drug-induced pancreatitis is often diagnosed only after ruling out the more common causes of pancreatitis such as gallstones, coupled with symptomatic relief and normalisation of blood tests on stopping the causative drug. We describe a case involving a 31 year old lady with a history of Crohn’s disease presenting with acute abdominal pain, raised WCC and markedly elevated amylase levels 4 weeks after commencing Pentasa (5-ASA) for Crohn’s disease. Two years later, after being commenced on Azathioprine, the patient was again readmitted with identical symptoms with raised amylase and WCC. This case report highlights the importance of considering drug induced pancreatitis in patients on 5-ASA and Azathioprine.

1. CASE REPORT
AP is a 31 year old lady who is normally fit and well with a family history of Crohn’s disease. She presented with a 3 month history of lower abdominal cramping pain associated with loose stools up to four times daily, no rectal bleeding and some weight loss. She complained of no other extra-intestinal symptoms. Her blood tests revealed elevated CRP, ESR and platelet count. She subsequently underwent a flexible sigmoidoscopy which showed an erythematous mucosa, patchy neovascularisation and mild ulceration in the distal sigmoid colon, however, histological analysis of the biopsies taken from the sigmoid colon and rectum were of normal mucosa. A barium meal and follow through was normal. Clinically the suspicion of Crohn’s disease was high but at the time of the consultation the patient was asymptomatic hence was managed conservatively. Ten months later AP presented with an acute flare up of Crohn’s disease, which was based on a white cell study. She was commenced on a reducing course of Prednisolone and Pentasa (5-ASA), but 4 weeks later presented to the Emergency department complaining of severe sharp abdominal pain that radiated to her back with nausea but no vomiting. On examination she was found to be tachycardic but otherwise stable. Her abdomen was soft, tender in the right upper quadrant but no guarding and normal bowel sounds. The rest of the examination was unremarkable. Initial clinical investigations revealed an elevated WCC (20.97x10^9/L), Platelets (544x10^9/L) and Amylase levels (724U/l- figure 1); liver function tests were unremarkable. A diagnosis of acute pancreatitis was made based on elevated serum amylase. She was commenced on Intravenous fluids and antibiotic therapy. Pentasa was discontinued as this was thought to be the cause of her acute pancreatitis. She made a complete recovery with normalisation of amylase 7 days after stopping the drug. She was discharged home on a reducing course of steroids. She suffered with 2 further flare ups of her Crohn’s disease in the next year which settled on reducing courses of Prednisolone.

Two years after her initial hospitalisation, she was commenced on Azathioprine 75mg daily as a steroid-sparing agent for maintenance of remission for managing her Crohn’s Disease. Three weeks later she was readmitted with a week’s history of epigastric pain that radiated through to her back with associated nausea, very similar to her previous presentation. On examination, her abdomen was soft with tenderness over the epigastric area on palpation but no guarding or rebound tenderness. Bowel sounds were normal and the rest of the examination was unremarkable. Initial blood tests showed elevated WCC (13.1 x10^9/L), Platelets (587 x10^9/L), Amylase (686U/L- figure 1) and mild hypoalbuminaemia (34g/L). A diagnosis of acute pancreatitis was made and an ultrasound was once again normal. The patient made a full recovery on stopping the Azathioprine and was then discharged home. Subsequently, the patient’s Crohn’s disease has been kept quiescent with maintenance infliximab infusions and a low residue diet and she has had no further episodes of pancreatitis.
2. DISCUSSION
To our knowledge this appears to be the first case report of a patient developing acute pancreatitis after administration of 5 ASA and Azathioprine on two separate occasions. There have been a few case reports of acute pancreatitis induced by 5-ASA\textsuperscript{1,2,3} within 4 weeks of starting treatment and one case report of a patient developing a relapse of acute pancreatitis after Azathioprine was stopped and 5 ASA restarted\textsuperscript{4}.

According to the British national formulary\textsuperscript{5}, acute pancreatitis is classified as a rare side effect of both Azathioprine and Aminosalicylates. 2\% of all cases of acute pancreatitis are thought to be secondary to drugs\textsuperscript{6}. In patients with inflammatory bowel disease, Azathioprine or Mesalazine\textsuperscript{7} are the agents contributing to drug induced pancreatitis in 67\% of cases.

Although the mechanism is uncertain, it has been suggested that it may be due to unpredictable systemic absorption of the drug leading to a hypersensitivity reaction\textsuperscript{2,8} in certain individuals. Furthermore, Decocg et al\textsuperscript{1} proposed that all derivative forms of 5-ASA have the potential to cause acute pancreatitis suggesting it may be due to a systemic response secondary to the drug. Despite numerous case reports, a population and case controlled study in Denmark concluded that there was no increased risk of acute pancreatitis in IBD patients when treated with 5-ASA or sulfasalazine\textsuperscript{9}.

The incidence of Azathioprine induced pancreatitis is estimated to be around 0.4\%\textsuperscript{10}. The same study also showed that 1 per 659 patients treated with Azathioprine will suffer from acute pancreatitis each year. Most cases of Azathioprine induced pancreatitis are in patients with inflammatory bowel disease\textsuperscript{11}, in particular 5\% of Crohn’s disease patients treated with Azathioprine will experience acute pancreatitis\textsuperscript{11,12}. Furthermore, acute pancreatitis is one of the more common causes for the withdrawal of Azathioprine in IBD patients\textsuperscript{11}. The increased susceptibility in IBD patients to Azathioprine induced pancreatitis\textsuperscript{13} have previously been suggested to be due to pancreatic autoantibodies\textsuperscript{14} but this is still unknown.

Both Aminosalicylates and Azathioprine are drugs that are often used to treat IBD. The more common side effects of Aminosalicylates include diarrhoea, vomiting, nausea, abdominal pain and headaches; whilst those for azathioprine include hypersensitivity reactions, bone marrow suppression, cholestatic jaundice and liver impairment. Currently, patients being treated with Aminosalicylates will require renal function monitoring before and after 6-8 weeks of starting treatment. Those on Azathioprine require weekly FBC monitoring for the first 4 weeks and a LFT at 6 weeks. With an increasing number of case studies reporting drug induced pancreatitis secondary to Aminosalicylates and Azathioprine often within 1 month, monitoring of the patient’s amylase level at 4 weeks or
earlier is warranted to prevent morbidity and mortality from acute pancreatitis. In addition, further IBD population studies are warranted to assess whether patients with Crohn’s disease are more susceptible to developing drug induced pancreatitis compared to their UC counterparts.

3. REFERENCES


