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Case Report

AZATHIOPRINE INDUCED ACUTE PANCREATITIS IN A CASE OF PHOTOALLERGIC CONTACT DERMATITIS

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ABSTRACT

Drug toxicity is a well-known cause of non-alcohol, nonbiliary acute pancreatitis. Azathioprine is a definite cause of drug induced pancreatitis, especially in patients with crohn's disease and following transplantation. The disease course is usually mild and self remitting with withdrawal of the drug. We are reporting a case of azathioprine induced pancreatitis in a patient with Photo-allergic dermatitis.

INTRODUCTION

Acute pancreatitis is an inflammatory disease of the pancreas with protean manifestations varied from mild pain abdomen to life threatening event. There are many risk factors for acute pancreatitis, among which most widely known are gallstones and alcohol abuse. Although drugs are considered as potential risk factors for acute pancreatitis, but have received relatively little attention in the medical literature. The pathogenesis of drug-induced acute pancreatitis has not been clarified yet**.** Azathioprine is a purine analog immuno-suppressant (prodrug of 6- Mercaptopurine) acts by inhibiting DNA synthesis used in various diseases such as inflammatory bowel disease (IBD), post-transplantation, vasculitis, autoimmune hepatitis. Overall 1.4-1.6% cases of acute pancreatitis are thought to be secondary to azathioprine. (Bermejo F., *et al*. 2008) Though the association of pancreatitis with azathioprin use has been described in relation with crohn's disease, post transplant patients and chronic active hepatitis, to the best of our knowledge, there is no report in the literature of the development of pancreatitis with the use of this molecule in patient with photoallergic contact dermatitis. With this background we report from India a case of acute pancreatitis associated with the use of azathioprin.

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Case Report

A 69 year old female who is known case of hypertension (on amlodepine and telmisartan) with hypothyroidism (on thyroid supplementation) for 10 years, having multiple white maculo-papular lesions over both hands,

Abdomen and lower limbs diagnosed as Photo-allergic dermatitis 3 months back for which she was put on steroids (prednisone) and azathioprine. Gradually, she got improved from dermatitis, but continuing medications as before. She presented with low grade fever, severe sharp epigastric pain radiating to back with 4-5 episodes of vomiting since last 8 days. There was no history of Diabetes Mellitus, Peptic ulcer or Gall bladder disease. She was non alcoholic. On physical examination, her abdomen was soft, tender in epigastric region with no guarding and normal bowel sounds. Rest of the systemic examination was unremarkable. Blood biochemistry (Table 1) revealed raised serum amylase and lipase suggestive of acute pancreatitis with mild anemia and leukopenia. Other biochemical parameters (blood glucose, serum electrolytes and renal functions) were normal. The anti nuclear antibody (ANA) and Rheumatoid Factor were negative. The viral markers for HIV-AIDS and hepatitis B & C were non reactive.

Ultrasound abdomen shows no obvious abnormalities such as gall stones or pancreatic duct dilatation, Contrast Enhanced Computed Tomography (CECT) abdomen –shows structurally normal pancreas (might be the picture of interstitial pancreatitis in which CECT is normal with

microscopic necrosis). She was diagnosed clinically and biochemically as case of acute interstitial pancreatitis and commenced on intravenous fluids, analgesic and antibiotic therapy. Both prednisone and azathioprin were stopped. With this initial management**,** the symptoms subside over 3 days, with disappearance of abdominal tenderness and normalization of serum amylase and lipase (Table1). Rechallenge test with azathioprin could not be performed owing to patient's safety.

Table 1 Showing changes in hematological parameters during admission.

Laboratory Parameter (units)	Report			Reference values
	On admission	Day 3	On Discharge	
Haemogram				
Hemoglobin (gm/dL)	10.9	10.5	11.0	12-18
Total Leucocytic count ($x10^3/mm^3$)	3.40	3.80	4.20	4.0 – 11.0
Differential leucocytic count (%)				
Neutrophil	81	60	76	40-75
Lymphocyte	15	31	21	20-45
Monocyte	03	08	02	2-10
Eosinophil	01	01	01	1-6
Basophil	00	00	00	≤1
Platelet count ($x10^3/mm^3$)	250	260	280	150- 400
Erythrocyte Sedimentation rate (mm/h)	08	12	15	0-20
Serum Amylase (U/L)	232	124	68	20-96
Serum Lipase (U/L)	1691	578	178	3-43
Liver Function Tests				
Bilirubin (mg/dL)				
Total	0.9			0.3 – 1.3
Direct	0.3			0.1 - 0.4
Indirect	0.6			0.2 - 0.9
ALT (U/L)	61			7 - 41
AST (U/L)	39			12 - 38
Alkaline Phosphatase (IU/L)	110			30-120
Protein, total (g/dL)	5.7			6.3-8.2
Albumin (g/dL)	3.2			3.5-5.0
Globulin (g/dL)	2.5			1.5-3.0
Fasting lipid profile				
Total Cholesterol (mg/dl)	136			< 200
Tryglyceride (mg/dl)	174			53-150
Low density lipoprotein(mg/dl)	101			< 100
High density lipoprotein(mg/dl)	36			23-74
Renal Profile				
Serum Creatinine (mg/dL)	1.6	1.2		0.5 - 0.9
Blood Urea (mg/dL)	56	34		10-50
Sodium (meq/L)	142	138		135-145
Potassium (meq/L)	3.76	3.8		3.5-5.5
Calcium (mg/dL)	9.2	9.3		8.7 – 10.2
Blood Glucose, Random (mg/dL)	103	108		70-140
HIV I, II	Non Reactive			
HBsAg/ Anti HCV	Negative			

ALT = Alanine Aminotransferase; AST = Aspartate Aminotransferase;

DISCUSSION

Acute pancreatitis is an acute inflammatory process of pancreas with varying involvement of other regional tissues and remote organ systems. Gallstones (30-60%) continue to be leading cause of acute pancreatitis followed by alcohol (15-30%). Other risk factors include hyperlipidemia, hypercalcemia, ERCP, trauma and infections. In 10 to 25% of the patients with acute pancreatitis, no obvious risk factors are present. Drug toxicity is a well-known cause of acute pancreatitis (AP). The overall incidence probably ranges from between 0.1 and 2% of pancreatitis cases. (Balani AR., *et al* 2008) Although more than 500 drugs are implicated in pancreatitis, the magnitude of the risk of most of them remains largely unknown as mostly they are from case and anecdotal reports. (Nitsche C., *et al* 2012) The risk of acute pancreatitis in azathioprine exposed patients is reported to be around 1.4-1.6%.(Bermejo F., *et al*. 2008). Most cases of Azathioprine induced pancreatitis are in patients with inflammatory bowel disease, in particular 4.9% of Crohn's disease patients treated with Azathioprine will experience acute pancreatitis (Badalov N., *et al* 2007)

The pathogenesis of azathioprin induced pancreatitis is incompletely understood, but thought to be due to idiosyncratic reaction which is unpredictable, not dose dependent, and have a low incidence in human beings. Idiosyncratic reactions can be further divided further into those secondary to hypersensitivity reactions and those caused by the accumulation of a toxic metabolite or some intermediary injurious substance. Hypersensitivity reactions that occur with the use of azathioprin, are caused by an immunologic response of the host in response to the drug and tend to occur with a latency of 1–6 weeks after exposure. Classically, hypersensitivity reactions are accompanied by a rash, fever, joint pains, lymphadenopathy, and eosinophilia. Clinical course of drug-induced pancreatitis is usually mild, and improves in a short time with discontinuance of the drug. (Weersma RK., *et al* 2004)

Documentation of drug induced pancreatitis most secure if 1) Other causes of pancreatitis are ruled out,2) there is an appropriate interval between initiation of therapy and induction of pancreatitis (4-8 weeks for most of drugs),3) Symptomatic relief and normalisation of blood tests on stopping causative drug,4) there is clear mechanism of drug induced pancreatitis i.e drug causing hypertriglyceridemia causes pancreatitis 5) Appearance of pancreatitis on rechallenge. (Steinberg WM., *et al* 2016)

In our case, she was presented with acute pain abdomen with recurrent vomiting. She was on both azathioprin and prednisone tablets for her dermatological problem for last 6 months. We have excluded other possible causes of pancreatitis. She improved clinically with disappearance of abdominal pain and normalisation of pancreatic enzymes after withdrawal of azathioprin. It can be concluded that there is a temporal relationship between azathioprin use and acute pancreatitis and simultaneously there is marginal increase in total leukocyte and hemoglobin on withdrawal of azithromycin which suggests bone marrow suppression is one of complication. Rechallenge test could not be done as patient was not giving consent for it. Reason behind the withdrawal of prednisone is possibility of synergistic effect of corticosteroid with azathioprin. Although corticosteroid

induced pancreatitis has been reported in different case series, the association is weak and questionable.

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