Azathioprine induced pancreatitis, polyarthritis and panniculitis (PPP) syndrome in a patient with Crohn's disease

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Abstract

Azathioprine and 6-mercaptopurine have been widely used for maintenance of remission in patients with inflammatory bowel disease. The use of thiopurines is associated with multiple adverse effects including dose dependent cytopenias or idiosyncratic reaction. We report about a case of azathioprine related pancreatitis associated with polyarthralgia and panniculitis. Pancreatitis, polyarthritis and panniculitis (PPP) syndrome is an uncommon phenomenon which may accompany a number of pancreatic diseases including acute or chronic pancreatitis or pancreatic malignancy. To the best of our knowledge, this is the first report of Azathioprine related PPP syndrome. (Acta gastroenterol. belg., **2020**, 83, **87-89**).

Key words : panniculitis, pancreatitis, thiopurine, Crohn's disease, inflammatory bowel disease, azathioprine

Introduction

Azathioprine and 6-mercaptopurine have been widely used for maintenance of remission in patients with inflammatory bowel disease. They belong to the purine analog group of drugs which act by inhibiting de novo purine synthesis as well as by interfering with the incorporation of nucleic acids during extension of DNA and RNA molecules. This leads to inhibition of cell proliferation and is responsible for both, the therapeutic immunomodulatory action as well as the dose dependent side effects. Adverse reactions of azathioprine have been classified as dose dependent and independent. Dose dependent adverse reactions occur due to the inhibition of cellular proliferation and can manifest as cytopenia. Dose independent adverse effects are due to hypersensitivity reactions to azathioprine and its metabolites. There are a multitude of manifestations of idiosyncratic reaction including fever, hypotension, arthralgias, hepatitis, pancreatitis, pericarditis and skin manifestations (1).

PPP syndrome (polyarthralgia, panniculitis pancreatitis) has been described in literature in few case series and case reports. It has been associated with acute and chronic pancreatitis and with pancreatic adenocarcinoma. We now report a case of Azathioprine related PPP syndrome (2-6).

Case report

A 16-year-old male, who had history of loose stools and abdominal pain for the past one year was evaluated in the outpatient's department. The symptoms had been increasing and he had history suggestive of colicky abdominal pain. His computed tomographic (CT) enterography was suggestive of thickening in terminal ileum and increased mesenteric vascularity. He had elevated fecal calprotectin (866 ug/g) and C-reactive protein levels of 35 mg/dL. Subsequently he was taken up for colonoscopy which revealed narrowing at ileocecal junction and multiple ileal ulcers. The biopsies were consistent with Crohn's disease showing changes of chronicity in form of crypt distortion, mucodepletion and architectural distortion. The patient was started on Budesonide 9 mg daily and at 2 months treatment the patient had significant improvement and was started on Azathioprine 50 mg daily for maintenance. Five days after the initiation of Azathioprine, the patient complained of epigastric pain; joint pain involving both knee joints, elbow joints and carpometacarpal joints and nodular skin lesions over the dorsum of both legs (Figure 1). There was mild swelling without tenderness over the joints but the skin lesions were tender. His amylase (488 U/L,

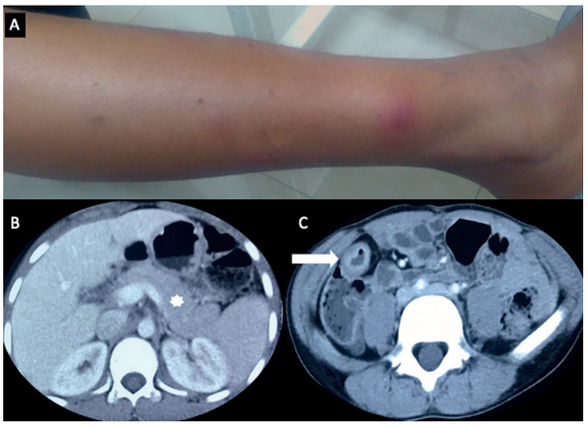

Figure 1. — A) Skin lesions consistent with panniculitis B) CT Showing bulky pancreas C) Mural thickening and stratification in terminal ileum.

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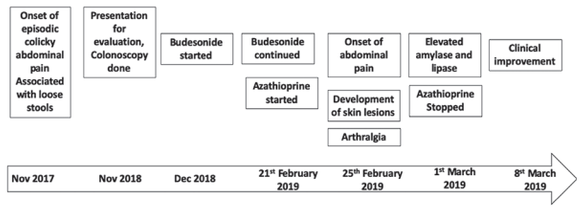

Figure 2. — Timeline of clinical presentation and course of events.

Normal< 100 U/L) and lipase levels (664 U/L, normal <60 U/L) were elevated. There was no history of alcohol intake, any other drug intake or recent trauma to the abdomen. USG showed no evidence of gall stones and the common bile dutc was normal. Contrast enhanced CT abdomen was done. It revealed a bulky pancreas with loss of lobularity (Figure 2A). The Balthazar was B and CT severity index was 1. There were no calcifications or other changes of chronic pancreatitis on CT imaging. The CT also showed mural stratification and thickening of terminal ileal loops (Figure 2B). CRP at presentation was 22 mg/dL. There was no evidence of hypercalcemia, hypertriglyceridemia or hyperparathyroidism. IgG4 levels were normal. A diagnosis of azathioprine related pancreatitis, panniculitis and polyarthralgia was established and the drug was stopped. The molecular testing for Thiopurine S-methylytransferase (TPMT) (c238G>C, c.460 G>A, c.719 A>G, c.719 A.G) Inosine triphosphate pyrophosphatase (ITPA) (c.94C>A) and Nudix hydrolase 15 (NUDT15) (c415 C>T) were non-contributory.

Subsequently the patient was managed conservatively. Budesonide was continued as before. Epigastric pain subsided over the next 4-5 days. Joint pain also subsided simultaneously while the skin lesions healed over the next two weeks. Figure 2 shows the time line and course of events. The patient had refused skin biopsy and a re-challenge was not done. We also assessed the causality using the Naranjo score which uses information of previous conclusive reports, conclusive evidence of adverse effect, temporal association with drug intake, effect of discontinuation and rechallenge, if any. The Naranjo score for azathioprine induced pancreatitis for the present case was 7 which suggests a probable causality (Table 1) (7).

Discussion

Pancreatitis, polyarthritis, panniculitis (PPP) syndrome is, as the name reveals, a constellation of symptoms involving multiple systems. It has been reported as early as in the 1960s (8). It was found to be associated with acute pancreatitis, chronic pancreatitis as well as pancreatic carcinoma (2-6). Of all the pancreatic malignancies it has been most often associated with pancreatic acinar cell carcinoma (2). Two third of the patients with PPP syndrome may be have no abdominal symptoms initially, which can lead to a delay in diagnosis (3) Joint involvement can occur as symmetric or asymmetric polyarthritis and usually affects knee, ankle, carpometacarpal joints although any joint can be involved. Skin lesions are nodular and typically occur over the lower extremities. They may or may not be tender and can erupt occasionally (1,3-5). There are two different hypothesis which explain the pathogenesis of this syndrome. One hypothesis is that the release of pancreatic enzymes leads to lipolysis and necrosis in distant tissue (3,5). Another hypothesis is that synthesis of lipase by local adipose tissue leads to lipolysis and increased concentration of free fatty acids, which trigger further activity (5,6).

Azathioprine is an immunomodulator which is used in maintenance therapy for both ulcerative colitis and Crohn's disease. However, adverse effects are substantial and can occur in up to 60 % patients (9,10). Azathioprine related side effects are seen more frequently in patients with IBD and other rheumatological diseases as compared to post transplant patients (11). In a cohort study by Macaluso et al 63.2 % patients discontinued azathioprine over a period of 32 months. Switching to 6-MP was done in 44 % cases. However, in 80% of those cases too, the drug had to be stopped due to adverse effects (9). In the retrospective study by Avallone et al, pancreatitis occurred in 13 out of 302 cases whereas erythema nodosum and arthralgia only occurred in one case (10). There have been multiple case reports of erythema

Table 1. — Naranjo score for the adverse event in the present cas

1,	Are there previous conclusive reports on this reaction?	Yes [+1]
2.	Did adverse event appear after the suspected drug was given?	Yes [+2]
3.	Did the adverse reaction improve when the drug was discontinued or a specific antagonist was given?	Yes [+1]
4.	Did the adverse reaction appear when the drug was re-administered ?	Do not know or not done [0]
5.	Are there alternative causes that could have caused the reaction?	No [+2]
6.	Did the reaction reappear when a placebo was given?	Do not know or not done [0]
7.	Was the drug detected in any body fluid in toxic concentrations?	Do not know or not done [0]
8.	Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	Do not know or not done [0]
9.	Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	Do not know or not done [0]
10.	Was the adverse event confirmed by any objective evidence?	Yes [+1]
	→ Naranjo Score	7
	Adverse Drug Reaction	PROBABLE

nodosum in patients on azathioprine and it is considered to be an idiosyncratic hypersensitivity reaction (12-14). A case of erythema nodosum and pancreatitis in a patient on azathioprine has also been reported (13). Symptoms recurred on rechallenging with the drug as well as after switching to 6-MP. Hence re-challenging is no longer recommended (12,15). The etiology of pancreatitis and rash in patients on azathioprine has not been elucidated. It can occur in up to 30% cases and cannot be predicted by polymorphisms in TPMT enzyme. Inosine triphosphate pyrophosphatase (ITPase) deficiency results in the benign accumulation of the inosine nucleotide ITP. 6-thio ITP get accumulated in patients on azathioprine which may be toxic. Polymorphisms in ITPA gene had significant association with occurrence of flu like symptoms, rash and pancreatitis (16). However the testing for common polymorphisms for these genes was non-contributory.

Our case presented with symptoms of pancreatitis, erythema nodosum and polyarthralgia within a week of initiating azathioprine therapy. Erythema nodosum and arthralgias are known extra intestinal manifestations of Crohn's disease. However, these symptoms are unlikely to be a part of extra intestinal manifestations of Crohn's disease as the patient was in remission when these symptoms occurred and there was a clear temporal association with initiation of Azathioprine and absence of bowel symptoms. Abatement of symptoms after stopping the drug further re affirmed our diagnosis and the elevated amylase and lipase levels confirmed our suspicion of a PPP syndrome. To our knowledge, this is the first case of PPP syndrome occurring as an adverse effect to azathioprine.

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Conflict of interest

None.

Written informed consent to publish was taken from the patient's kin.

Author contribution

SM : manuscript draft, literature search and final approval ; SG : manuscript draft and final approval ; RM : patient care, intellectual content, final approval ; AP, PB : manuscript revision, intellectual content, final approval ; VS : manuscript writing ; revision ; patient care and final approval.

References

1. PUDIPEDDI A., KARIYAWASAM V., HAIFER C., BARATY B., PARAMSOTHY S., LEONG R.W. Safety of drugs used for the treatment of Crohn's disease. *Expert. Opin. Drug. Saf.,* 2019, **18** : 357-367.
2. KLIMSTRA D.S., HEFFESS C.S., OERTEL J.E., ROSAI J. Acinar cell carcinoma of the pancreas. A clinicopathologic study of 28 cases. *Am. J. Surg. Pathol.,* 1992., **16** : 815-37.
3. NARVÁEZ J., BIANCHI M.M., SANTO P., DE LA FUENTE D., RÍOS-RODRIGUEZ V., BOLAO F., *et al.* Pancreatitis, Panniculitis, and Polyarthritis. *Semin. Arthritis. Rheum.,* 2010, **39** : 417-23.
4. AZAR L., CHATTERJEE S., SCHILS J. Pancreatitis, polyarthritis and panniculitis syndrome. *Joint. Bone. Spine*., 2014, **81** : 184.
5. LOVERDOS I., SWAN M.C., SHEKHERDIMIAN S., AL-RASHEED A.A., SCHNEIDER R., FISH J.S., *et al.* A case of pancreatitis, panniculitis and polyarthritis syndrome: Elucidating the pathophysiologic mechanisms of a rare condition. *J. Pediatr. Surg. Case. Rep*., 2015, **3** : 223-6.
6. PRICE-FORBES A.N., FILER A., UDESHI U.L., RAI A. Progression of imaging in pancreatitis panniculitis polyarthritis (PPP) syndrome. *Scand. J. Rheumatol*., 2006, **35** : 72-4.
7. NARANJO C.A., BUSTO U., SELLERS E.M., SANDOR P., RUIZ I., ROBERTS E.A., *et al.* A method for estimating the probability of adverse drug reactions. *Clin. Pharmacol. Ther.,* 1981, **30** : 239-45
8. MULLIN G.T. Arthritis and Skin Lesions Resembling Erythema Nodosum in Pancreatic Disease. *Ann. Intern. Med*., 1968, **68** : 75.
9. MACALUSO F.S., RENNA S., MAIDA M., DIMARCO M., SAPIENZA C., AFFRONTI M., *et al.* Tolerability profile of thiopurines in inflammatory bowel disease: a prospective experience. *Scand. J. Gastroenterol.,* 2017, **52** : 981-7.
10. AVALLONE E.V., PICA R., CASSIERI C., ZIPPI M., PAOLUZI P., VERNIA P. Azathioprine treatment in inflammatory bowel disease patients: type and time of onset of side effects. *Eur. Rev. Med. Pharmacol. Sci.*, 2014,**18** : 165-70.
11. WEERSMA R.K., PETERS F.T.M., OOSTENBRUG L.E., VAN DEN BERG A.P., VAN HAASTERT M., PLOEG R.J., *et al.* Increased incidence of azathioprine-induced pancreatitis in Crohn's disease compared with other diseases. *Aliment. Pharmacol. Ther.,* 2004, **20** : 843-50.
12. GONZÁLEZ-OLIVARES M., KHEDAOUI R., MARTÍNEZ-MORÁN C., BORBUJO J. Azathioprine-Induced Hypersensitivity Reaction Presenting as Erythema Nodosum. *Actas. Dermo-Sifiliográficas.,* 2017, **108** : 591-3.
13. DE FONCLARE A.L., KHOSROTEHRANI K., ARACTINGI S., DURIEZ P., COSNES J., BEAUGERIE L. Erythema Nodosum–like Eruption as a Manifestation of Azathioprine Hypersensitivity in Patients With Inflammatory Bowel Disease. *Arch. Dermatol.,* 2007, **143** : 744-8.
14. BIDINGER J.J., SKY K., BATTAFARANO D.F., HENNING J.S. The cutaneous and systemic manifestations of azathioprine hypersensitivity syndrome. *J. Am. Acad. Dermatol.,* 2011, **65** : 184-91.
15. LAI S-W., WANG Y-C., WANG C-H., HUANG T-Y. Acute pancreatitis and erythema nodosum associated with azathioprine. *QJM*., 2012, **105** : 363-4.
16. MARINAKI A.M., ANSARI A., DULEY J.A., ARENAS M., SUMI S., LEWIS C.M., *et al.* Adverse drug reactions to azathioprine therapy are associated with polymorphism in the gene encoding inosine triphosphate pyrophosphatase (ITPase). *Pharmacogenetics.,* 2004, **14** : 181-7.