Azathioprine induced colitis : a case report and review of the literature

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Abstract

We report a case of an allergic hypersensitivity reaction on azathioprine presenting with colitis. Allergic reactions on azathioprine are common in patient with inflammatory bowel disease. The clinic of the allergic reaction on azathioprine in our patient was atypical in the way it mimicked an acute exacerbation of inflammatory bowel disease. The pathogenesis of the allergic reaction is still unclear. Although re-challenge can be life-threatening and should always be done with precautions, it may definitively proof the causal association with the drug and decide for definitive cessation In allergic reactions there is no link with TPMT activity but other genetically predispositions are proposed. (Acta gastroenterol. belg., **2007**, 70, **302-305**).

Introduction

Allergic reactions on azathioprine are common in patient with inflammatory bowel disease. We report a case of an allergic hypersensitivity reaction on azathioprine presenting with colitis. The clinic of the allergic reaction on azathioprine in our patient mimicked an acute exacerbation of inflammatory bowel disease.

Case report

A 54-year-old Caucasian female patient presented with a history of epigastric complaints. There was no diarrhea nor fever. Upper gastrointestinal endoscopy was negative for peptic lesions and therapy with a proton pump inhibitor did not bring any relief. No other medication was taken. The family history was not contributive. She was a non-smoker. From the personal medical history we withhold sectio cesarae, trigeminus neuralgia and slow transit constipation. Further investigations with small bowel follow through revealed that her epigastric complaints were caused by a subobstruction due to a segmentary stricture of the terminal ileum over a length of 20 cm. On ileocolonoscopy and subsequent histopathology a Crohn ileitis without colitis was diagnosed. Laboratory tests showed no inflammation. Because of the mechanical obstruction a right hemicolectomy was performed. Postoperative no preventive medication was given. Six months after, a repeat ileocolonoscopy revealed an endoscopic recurrence with a Rutgeerts' score i3 (diffuse aphtous ileitis with diffusely inflamed mucosa). Azathioprine (AZA) 150 mg/day (2.5 mg/kg/day) orally was started. One week after the onset of azathioprine the patient developed fever, fatigue, diarrhea, anorexia and epigastric pain. On laboratory tests elevated inflammatory parameters (C-reactive protein : 242 mg/liter) were seen. Sigmoidoscopy showed erythema with a loss of vessel sign and without ulcerations in the colon. Coprocultures remained negative. Pathology showed a diffuse inflammation without arguments for Crohn colitis nor ulcerative colitis. There were no indications for opportunistic infections or tuberculosis. AZA was interrupted and the patient recovered spontaneously. Eighteen months later, the patients developed a clinical relapse. Ileocoloscopy again showed Crohn ulcers in the neoterminal ileum with a macroscopically and microscopically perfectly normal colon (Fig. 1). Rechallenge with AZA was done with careful clinical follow-up of the patient. After ingestion of 50 mg/day of AZA on two consecutive days the patient again developed fever, diarrhea and fatigue. Endoscopic investigation showed a loss of vessel sign in the colon without ulcerations. The colon biopsy shows diffuse colitis with cryptitis and focal partial crypt destruction (Figs. 2A and 2B). Given the earlier hypersensitive reactions on AZA, we stopped the AZA therapy instantly and definitively. A few weeks later intramuscular methotrexate (MTX) (25 mg weekly) treatment was started with good clinical improvement and no side effects. Until now – 18 months later – the patient remains in clinical and endoscopic remission under this therapy. The most common variants in the thiopurine methyl-S-methyltransferase (TPMT) -TPMT*2 (gene G238C), TPMT*3A (gene G460A, A719G), TPMT*3B (gene G460A) and TPMT*3C (gene A719G)- were tested in this patient but the patient was wild type for all of them.

Discussion

The use of AZA in inflammatory bowel disease (IBD) was first reported in 1969 (1). It represented a significant therapeutic advance and is still widely prescribed in

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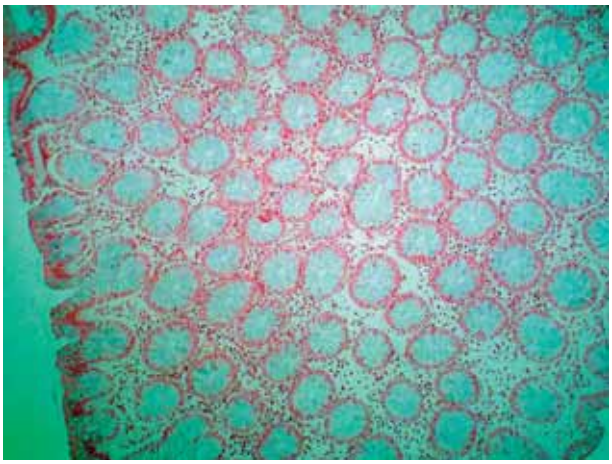

Fig. 1. — Overview picture of normal colon biopsy prior to the administration of Azathioprine (Haematoxylin Eosin 100×).

IBD. However, the drug has side effects and discontinuation of therapy is necessary in 9 to 25% of the patients (2-5). There are 2 main types of adverse reactions : which can be divided in non-allergic (dose-dependent, late, metabolism-related) and allergic (dose-independent, early, idiosyncratic) side effects (2-4, 6-8). The metabolism of the thiopurine drugs is complex (Fig. 3). Azathioprine is a pro-drug that is converted to 6-Mercaptopurine (6-MP) via a nonenzymatic nucleophilic attack by sulfhydryl-containing compounds such as glutathione present in erythrocytes and other tissues (9). 6-MP is further metabolized by three competing enzymatic pathways (Fig. 1). The xanthine oxidase pathway witch produces a biologically inactive metabolite. The second pathway produces 6-methylmercaptopurine (6-MMP) by the action of TPMT. The third pathway leads to the production of 6-Thioguanine nucleotides (6-TGN) following three consecutive steps (3,9-12).

A lot of the non-allergic adverse reactions relate to the TPMT enzyme activity which is under genetic control. Approximately 1 in 300 patients are TPMT-deficient, 6 to 11% of the population has an intermediate TPMT activity and 89 to 94% has normal activity (2-3,6,9-10). TPMT deficiency has been shown to be a cardinal player in the development of myelosuppression (2,12-18). Although there is a link between myelosuppression, the level of TPMT activity and the serum level of 6-TGN in patients treated with AZA or 6-MP, TPMT does not explain everything. Myelosuppression is the most frequent non-allergic side effect. AZA-induced hepatotoxicity on the other hand has also been linked to a high activity of TPMT and the accumulation of 6-MMP (2,12).

The second class of adverse effects are considered allergic. The most common presentation of an allergic reaction is a hypersensitivity reaction. It occurs in 2.7 to 25% of the patients with IBD treated with AZA (7-8,11). Symptoms are fever, joint and back pain, skin rash, diarrhea and nausea (4,6-8,11,19,20). The hypersensitivity reaction can also present itself by involvement of one specific organ with systemic symptoms. There are conflicting data about the causal molecule. In several reports it is believed that the hypersensitivity reaction is caused by the methyl-nitro-thioimidazole molecule which is split from AZA by glutathione-S-transferase in the first metabolisation step (2,5,8,11,19-22). This is supported by the fact that some patients with proven hypersensitivity to AZA did not react after re-challenge with 6-MP (5,19,23). Hypersensitivity reactions to 6-MP are also described (8,11). The administration of 6-thioguanine (6-TG) was suggested as alternative for 6-MP and AZA but is not recommended for clinical use given the hepatotoxicity which is associated with use of this drug. It is unclear which type of hypersensitivity reaction is the basis for the symptoms. Most reports

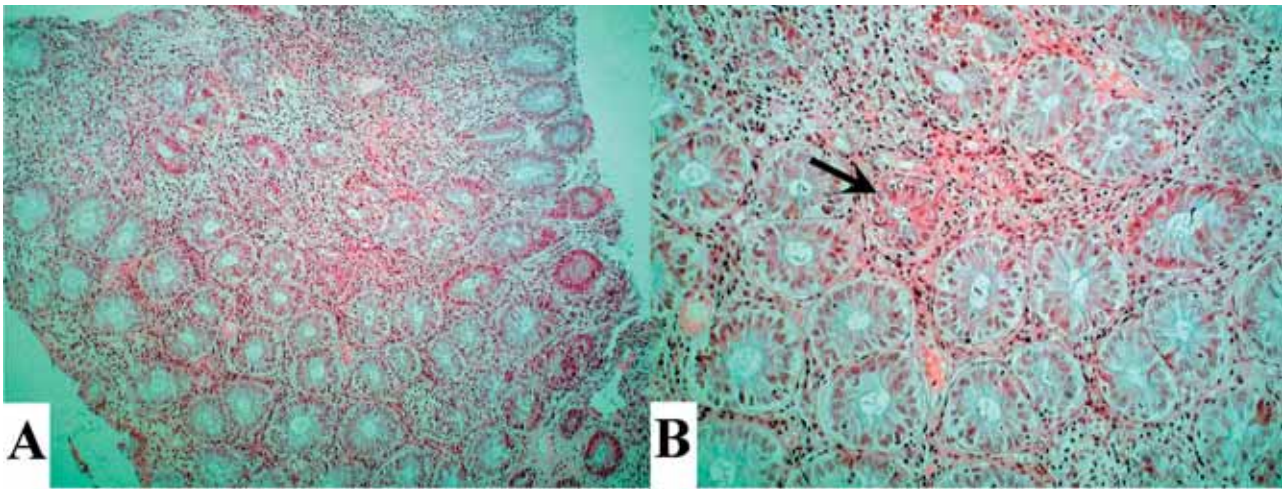

Fig. 2. — (A) Diffuse colitis developed after ingestion of twice 50 mg of Azathioprine (Haematoxylin Eosin 100×). (B) High power magnification revealed cryptitis (arrow) with focal partial crypt destruction. There is a mixed infiltrate of inflamatory cells, including a prominent component of neutrophils (Haematoxylin Eosin 200×).

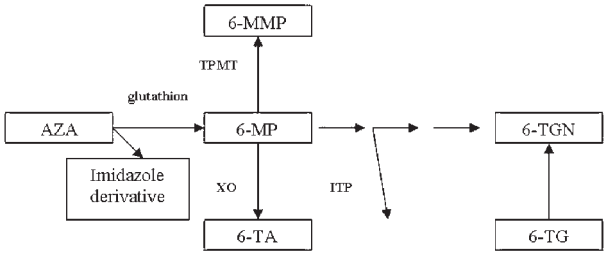

Fig. 3. — Simplified pathway of thiopurine metabolism. AZA, azathioprine ; 6-MP, 6-mercaptopurine ; 6-MMP, 6-methyl-mercaptopurine ; 6-TA, 6-Thiouric acid ; 6-TGN, 6-thioguanine nucleotides ; 6-TG, 6-thioguanine ; TPMT, thiopurine methyl-S-methyltransferase ; XO, Xanthine oxidase ; ITP, Inosine triphosphate pyrophosphatase.

describe a type 1 reaction, where a metabolite functions as a hapten, eliciting an Ig E mediated mast cell degranulation (11,22). Other reports prefer a type 3 reaction, because the hapten binds initially with a protein molecule (20). For more delayed hypersensitivity reactions such as pancreatitis a cell mediated immunological reaction (type 4) is thought to play an important role (4,11, 22). Probably several immunological mechanisms may be involved. An underlying genetic predisposition to hypersensitivity reactions is also proposed. Inosine triphosphate pyrophosphatase polymorphism is associated with allergic reactions (rash and pancreatitis) (25).

For our patient we consider the reaction on AZA as an allergic reaction, since it occurred early, was dose-independent and idiosyncratic with the involvement of a single organ. Furthermore, symptoms disappeared spontaneously after cessation of the drug and a careful re-challenge with AZA produced the same symptoms. The hypersensitivity reaction in our patient was not typical. There was no skin rash, arthralgia or muscle pain. The presenting symptom was a severe colitis with fever and diarrhea mimicking an acute exacerbation of inflammatory bowel disease. An infectious cause was excluded. There was an equal but earlier reaction after re-challenge. To our knowledge this is the first case report of a hypersensitivity reaction to AZA presenting as a colitis described in a patient with IBD without colorectal involvement. This side effect of AZA therapy is important because of its atypical presentation and the importance of a correct management. It is difficult to differentiate between allergic reactions, infections and underlying IBD. Recognition is important because re-challenge can cause life threatening diarrhea and shock (6,19).

In a patient presenting with hypersensitivity reactions on AZA further therapeutic options are restricted. In our patient we started therapy with intramuscular MTX with good clinical effect. Some authors describe a successful desensitization to AZA (26,27) and 6-MP (8) resulting in tolerance and therapeutic success, however, we feel this cannot be recommended. Starting biological therapy with anti-TNF agents however, must be considered in patients with severe disease or patients not-responding or intolerant to MTX.

Conclusion

Allergic reactions on AZA are common in patient with IBD. The presentation is mostly with a typical hypersensitivity reaction, but can be atypical with involvement of a single organ. The pathogenesis of the allergic reaction is still unclear. Although re-challenge can be life threatening and should always be done with precautions, it may definitively proof the causal association with the drug and decide for definitive cessation. In allergic reactions there is no link with TPMT activity but other genetically predispositions are proposed.

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