

Myelotoxicity Induced By Allopurinol

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Abstract

Patients with a severe inflammatory bowel disease or who have corticoid dependence should be treated by thiopurine drugs, azathioprine and 6-mercaptopurine. Although the drugs are usually well tolerated, adverse reactions can occur like bone marrow suppression which is dose-dependent and a delayed side effect requiring regular complete blood count monitoring. We describe a patient with ulcerative colitis who developed azathioprine-induced pancytopenia.

Keywords: Inflammatory bowel disease, thiopurine drugs, side effect, azathioprine-induced pancytopenia.

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INTRODUCTION

Thiopurines are analogues of hypoxanthine which inhibits the synthesis of DNA and RNA. They include 6-mercaptopurine, thioguanine and azathioprine. Azathioprine is the most used. It is a prodrug, whose active form is also a prodrug, 6-mercaptopurine, which is obtained after hepatic and erythrocyte metabolism. Its pharmacological action is dependent on the formation of 6-thioguanine metabolites. The haematological toxicity of azathioprine is well known to prescribers [1] it includes: Leukopenia; thrombocytopenia, an eosinophilia, isolated macrocytosis or anemia [1, 2] and in rarely cases bone marrow suppression which is the severe complication [3]. We describe a patient with ulcerative colitis who developed azathioprine-induced pancytopenia.

CASE REPORT

A 27 years old man, consulted for tenesmus and chronic bloody diarrhea in 2015. Signs of inflammation were revealed in the laboratory screen. Colonoscopy was done with finding of mild to moderate left-sided ulcerative colitis. The patient began to take mesalazine 4 g per day. One year later; a relapse with endoscopic finding of extensive, active colitis occurred. The patient was treated with prednisolone 60 mg a day and after a clinical remission the dose was gradually decreased. He was symptomatic at Prednisolone 10 mg. Due to the corticosteroid-dependent course of the disease, a decision to treat him with azathioprine was made associated to Prednisolone with a progressive decrease. Three months after starting treatment with azathioprine; the patient developed signs of septicemia with aregenerative

pancytopenia. Neutrophils were to 100 el/ mm³. The diagnosis of bone marrow suppression induced by azathioprine was suspected; Azathioprine was discontinued immediately and injections of neupogen with the administration of broad spectrum antibiotics, was made. The patient was asymptomatic after three days of treatment and had no pancytopenia. Azathioprine was arrested and was been under infliximab for the treatment of his extended ulcerative colitis.

DISCUSSION

Side effects of azathioprine are dose-independent (allergic reactions, idiosyncrasies) or dose-dependent (myelotoxicity, hepatitis, cancer) [4]. Bone marrow suppression is a potentially serious side effect of azathioprine treatment. It is largely dose-dependent and occurs in 2-25% patients as side effect during treatment with azathioprine (AZA) [5]. However, severe and unexpected myelosuppression, has also been reported when low to moderate doses (<2 mg/kg/day) of the drug were used. In these cases, the cytopenic patients are vulnerable to the development of sepsis that necessitates hospital admission for intensive care. Some studies have reported that TPMT genotype or activity does not predict the development of azathioprine-induced myelotoxicity [6]. On the other hand, some reports have suggested a substantial correlation between low enzyme activity and the development of myelotoxicity [7]. Colombel *et al.*, reported that assessment of the TPMT genotype or activity can reduce the risk of myelotoxicity in approximately one-third of patients [8].

The use of granulocyte macrophage colony-stimulating factor (GM-CSF) has a great impact in this side effect because it plays an important role in the modulation of cellular proliferation, differentiation, angiogenesis, and inflammation [8].

CONCLUSION

Systematic determination of TPMT activity or genotyping of the TPMT before the initiation of azathioprine treatment could prevent the occurrence of hematologic disorders such as bone marrow failure. In all cases, treatment with azathioprine requires weekly biological monitoring, with a blood count during the first eight weeks, then every three months. This attitude is benefic to detect azathioprine myelotoxicity. Immediate stop of azathioprine and the use of granulocyte macrophage colony-stimulating factor associated with antibiotics in the case of septicemia improve the prognosis.

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