

Case Report

Tremor as a Rare Undesirable Effect of Azathioprine in Remission Patient with a Pancolonic Ulcerative Colitis Disease

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Abstract: Here, we report a 18 year-old man presented with tremor. The patient had a history pancolonic ulcerative colitis and he had been on corticosteroid in degression and azathioprine (AZA). He had no history of other medications, herbal or alcohol; no other diseases were diagnosed and no family history of note. The patient presented 1 month after taking AZA 2 kg/mg/day Involuntary, rhythmic movements and twitching of hands. Physical examination was normal. Biological tests and Electromyogram (EMG) were in favor of a physiologic tremor which is probably of toxic origin, and retain the diagnosis of tremor secondary to adverse effects of AZA. The outcome was favorable the day after stopping AZA. Despite its rarity, the tremor remains a significant side effect due to the socioeconomic effect that it induces.

Keywords: Azathioprine, tremor, inflammatory bowel disease, side effects.

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INTRODUCTION

Azathioprine is the most widely used immunosuppressant in the treatment of inflammatory bowel disease (IBD); the effectiveness of this molecule remains very variable according to the studies varying between 5% to 70%. This variability is explained by a non-negligible proportion of discontinuation of treatment following the occurrence of adverse effects. These undesirable effects can be divided into 2 categories: dose-dependent undesirable effects linked to the accumulation of intracellular metabolites and which appear late with delays of up to years and immediate undesirable effects that appear in the days following the start of treatment. These 2 types of side effects are more found in patients with chronic inflammatory bowel disease compared to other indications (MS; PR; HAI).

The most reported side effects are hematological, digestive intolerance or pancreatitis to azathioprine except other much rarer side effects including tremor which is the subject of our work.

CASE REPORT

Here, we report the case of A.J an 18 year-old man A.J presented with tremor. The patient had a history pancolonic ulcerative colitis and he had been on corticosteroid in degression and azathioprine (AZA) treatment for 3 months. He had no history of other

medications, herbal or alcohol; no other diseases were diagnosed and no family history of note. The patient presented to his consultation 4 weeks after stopping the corticosteroid by dose reduction and remained on AZA 100 mg a day (2 kg/mg/day) for occurrence of repetitive and rhythmic involuntary movements of the hands. The intensity of the tremor aggravated 2h-3h after taking the treatment. On physical examination, the patient was hemodynamically stable and afebrile, with a blood pressure of 110/60 mm Hg, a pulse of 77 beats/ min. on the neurological examination the nerve function and motor and sensory skills were normal.

The blood count and other biochemical tests, including liver and kidney function, were normal. Serum electrolytes were within the normal range. The dosage of magnesemia and calcemia were normal as well as the level of vitamins (B6; B12; D) didn't reveal any abnormalities. Thyroid-function tests: TSH, T4, parathormone were normal. Electromyogram (EMG) was in favor of a physiologic tremor which is probably of toxic origin. One day after the patient stopped treatment the symptoms disappeared. Because of the need for immunosuppressant to maintain the remission of his ulcerative colitis we decided to switch to 6-Mercaptopurine with a wide controle.

DISCUSSION

Azathioprine is an antimetabolite drug having wide range of indications; of which predominantly listed are inflammatory bowel diseases: crohn, ulcerative colitis. Actually, the use of thiopurones has been frequently associated with several adverse effects, the most frequent of which are hematological, hepatic and pancreatic effects that often leads 2 [5, 6]. After absorption of AZA, it will be metabolized to PM, and will then lead to the formation of several metabolites, including 6-thioguanine nucleotides and 6-methylmercaptapurine ribonucleotides which are considered to be the most important metabolites [7].

In several studies, a high rate (38.9%) of treatment discontinuation was observed within the first 5 months, primarily because of side effects. This rate is in line with previous studies which reported discontinuation rates of approximately 30% within the first months [5, 8]. The high discontinuation rate underlines the potential impact of thiopurine-induced adverse events. As expected, gastrointestinal side effects were the most frequently reported adverse event and occurred in approximately 50% of the patients [10].

Other more rare side effects were observed such as the tremor subject of our study [14]. Very few studies have reported tremor as an adverse effect to azathioprine, the most recent is the report case of Fatih Karaahmet and All who reported a case titled " Tremor as dose dependent side-effect of azathioprine in remission patient with ileal Crohn's disease [3]".

It was about a 48-year-old woman who has been on Azathioprine for 2 months for ileal crohn's disease with onset of side effects such as tremor. Tremor occurs as dose dependent side-effect of AZA and after discontinued treatment it quickly disappears, which is exactly similar to our case report [4].

Some studies have investigated the benefit of switching from Azathioprine to Mercaptopurine in the event of adverse effects [9]. Although some patients were rechallenged after discontinuing the initial thiopurine, no detailed information was available to report on success rates of this switch.

However, monitoring of unwarranted side effects of long-term azathioprine accounts for monitoring of hematological parameters, and dipping of leukocyte especially lymphocyte count is considered an alarming feature for stopping the drug. Clinicians evaluating patient with Crohn's disease receiving AZA and exhibiting tremor should keep in mind that AZA can produce uncommon adverse reactions [10].

CONCLUSION

AZA has been widely used as an immunosuppressant. Adverse effects of AZA include fever, myalgia, diarrhea, nausea and vomiting, acute pancreatitis, and tremor were described in literature. Tremor is often seen in IBD patients receiving the drug, but rarely occurs under other indications.

The exact mechanism responsible for the AZA-induced tremor is still unknown. But the tremor occurs as a dose-dependent side effect of AZA and after stopping treatment it goes away within days.

Clinicians evaluating patient with IBD receiving AZA and exhibiting tremor should keep in mind that AZA can produce uncommon adverse reactions.

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