

Severe Muscular Weakness as an Isolated Symptom of Azathioprine Hypersensitivity

To the Editor:

Azathioprine (AZA), an analog of 6-mercaptopurine, has been used as a steroid-sparing agent in the treatment of inflammatory bowel disease (IBD) for over 30 years. Unfortunately, adverse effects including dose-dependent myelosuppression and dose-independent hypersensitivity reactions (fever, vomiting, arthralgia, myalgia, cutaneous reactions, pancreatitis, hepatitis, diarrhea) can result in discontinuation of the immunosuppressant therapy (Table 1).¹

We report a case of AZA hypersensitivity in a patient with IBD manifesting with the unusual symptom of profound muscular weakness.

A 55-year-old man with a long-standing, steroid-dependent, ulcerative pancolitis was admitted for a moderate to severe flare of the disease. After an effective induction treatment with steroids (prednisone 0.75 mg/kg), maintenance therapy was started with AZA (2.5 mg/kg).

About 2 weeks later the patient presented in the emergency room with mild arthralgia and severe muscular weakness resulting in inability to perform simple tasks such as lifting even light objects, sitting upright, and walking a few steps. Laboratory findings revealed only a slightly elevated white blood cell count (11,600/mm³) and a normal erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP).

First, it was suspected that these were likely due to an acute muscle disorder, such as myopathy, possibly steroid-induced, or due to extraintestinal

manifestation of ulcerative colitis. However, a specialist clinical and radiological evaluation showed no evidence of inflammation in the joints, so a rheumatologic disorder was ruled out. Moreover, a normal creatinine phosphate kinase and many previous steroid cycles suggested that his symptoms were less likely to be due to steroid-induced myopathy.

Furthermore, due to the temporal relationship of his symptoms with the commencement of immunosuppressant therapy, we suspected his muscular weakness to be an unusual manifestation of AZA hypersensitivity. Therefore, the drug was discontinued and this was followed by complete resolution of his symptoms.

One month later we tried a supervised rechallenge with AZA (0.75 mg/kg), which resulted in a recurrence of his symptoms and elevated white blood count (WBC) (13,200/mm³) within 24 hours.

Although symptoms of fever and arthralgia have been well described as an expression of AZA hypersensitivity in patients with IBD in the literature, to our knowledge very few cases document an isolated profound muscular weakness in patients with IBD.^{2,3}

Interestingly, these hypersensitivity reactions can sometimes manifest with clinical features similar to those of the underlying disorder, like diarrhea in a patient with IBD⁴ or joint pain in a case of rheumatoid arthritis.⁵ Usually, symptoms appear 2–4 weeks after the first exposure to the AZA and resolve on discontinuing the drug and reappear more severe and more rapidly on rechallenge.

The precise mechanism of these hypersensitivity reactions remains unclear. Hypersensitivity reactions seems to be unrelated to TPMT gene mutations and cannot be prevented by monitoring of TPMT activity. The imidazole component of AZA may be responsible for hypersensitivity reactions, so 6-mercaptopurine, its active metabolite, could be used safely in these patients.

Like other drugs, AZA could act on neuromuscular transmission by autoimmune mechanisms binding to acetylcholine receptors or triggering the formation

TABLE 1. Adverse Effects of Azathioprine.

Dose-dependent Adverse Effects	Dose-independent Hypersensitivity Reactions
Bone marrow suppression	Fever Vomiting Cutaneous reactions Pancreatitis Hepatitis Diarrhea Arthralgia Myalgia

of antibodies against these receptors.⁶ Another possible mechanism of AZA-induced muscular weakness may be related to a phosphodiesterase inhibition.

The diagnosis of AZA hypersensitivity should be considered in patients who have recently either initiated or increased their dosage of the immunosuppressant drug. The time course and presenting signs and symptoms support the diagnosis of AZA hypersensitivity, as does the patient response to rechallenge.

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