Case Report

Concomitant acute alopecia and profound bone marrow suppression: An unusual manifestation of azathioprine toxicity

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ABSTRACT

Azathioprine is a cytotoxic drug used frequently as a steroid-sparing agent in multiple dermatological diseases. Myelosuppression is known to occur with azathioprine, but severe pancytopenia and hair loss are uncommon. Hair loss usually occurs with long-term use, but sudden onset and rapidly progressive alopecia are extremely rare. In this report, we present an unusual case of a patient with chronic spontaneous urticaria, accompanied by elevated serum immunoglobulin E levels, who developed sudden-onset, rapidly progressing alopecia areata concurrent with azathioprine-induced bone marrow suppression. The patient's condition improved following discontinuation of azathioprine, with concurrent resolution of leukopenia and gradual hair regrowth, suggesting a temporal and possibly causative relationship between the drug and both the hematologic and dermatologic manifestations. This case emphasizes the unpredictable nature of immunomodulatory therapy and highlights a paradox wherein a drug intended to suppress autoimmune activity potentially triggers a separate autoimmune condition. It also emphasizes the importance of vigilant monitoring for both common and rare adverse effects during azathioprine therapy.

Key words: 6-mercaptopurine, Azathioprine, Immunoglobulin E, Myelosuppression, Thiopurine methyl transferase

Azathioprine is an immunosuppressive purine analogue used as a steroid-sparing agent to manage chronic inflammatory and autoimmune diseases. Its efficacy is proven in common dermatological diseases such as atopic dermatitis, chronic urticaria, and autoimmune blistering diseases. The drug acts by interfering with DNA synthesis in proliferating lymphocytes, thereby exerting cytotoxic effects. Although considered a safe immune-modulator, hematological complications like myelosuppression are well documented. While mild-to-moderate bone marrow suppression is relatively common, severe pancytopenia is a rare event. Alopecia, particularly of the telogen effluvium, is due to cumulative cytotoxic effects or nutritional deficiencies secondary to chronic immunosuppression [1]. Abrupt onset of alopecia areata (AA) during azathioprine therapy is exceedingly rare. AA is an autoimmune-mediated, non-scarring hair loss condition characterized by T-cell infiltration around hair follicles, resulting in localized or generalized hair shedding. The emergence of AA in the context of azathioprine use is a paradoxical manifestation due to activation of autoimmune pathways [2,3].

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We describe a clinically unusual and complex case of a patient with chronic spontaneous urticaria, accompanied by elevated serum immunoglobulin E (IgE) levels, who developed sudden-onset, rapidly progressing AA concurrent with azathioprine-induced bone marrow suppression. The patient's condition improved after discontinuation of azathioprine, with concurrent resolution of leukopenia and gradual hair regrowth, suggesting a temporal and possible causative relationship between the drug and both the hematologic and dermatologic manifestations. It is emphasized that vigilant monitoring is required for both common and rare adverse effects during azathioprine therapy.

CASE REPORT

A 43-year-old man presented with complaints of recurring episodes of transient erythematous, pruritic lesions, occurring almost every day, for the last year. He had received intermittent medication treatment for chronic urticaria for about 1 year.

On examination, his vital parameters were within normal limits. Dermatological examination revealed multiple discrete to confluent erythematous plaques distributed over the trunk and extremities. The lesions

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lasted for 2–3 days, and then faded away over a period of time.

The hematological and biochemical parameters were not conclusive. In the absence of any inciting factor for the episodes of urticaria, he was managed as chronic idiopathic urticaria, with antihistaminics and montelukast. Further evaluation revealed raised IgE, 947 KUA/L (normal <64 KUA/L), and the autologous serum skin test was positive.

The patient was started on oral Azathioprine 100 mg daily, and antihistaminics were continued. After 2 weeks of initiation of therapy, the relevant hematological and biochemical parameters were within normal limits. The response to treatment was adequate with reduced urticarial episodes.

After 1 month of initiation of therapy, the patient reported to the emergency department of the hospital with complaints of sudden onset of hair loss and fever (Fig. 1). The patient was hospitalized, and the investigation revealed severe myelosuppression along with lobar pneumonia (Fig. 2). He was then managed with broad-spectrum antibiotics and granulocyte colony-stimulating factor (G-CSF). Due to rapidly progressive hair loss, the scalp was completely bald within 7 days. The hematological and biochemical parameters during the phase of hospitalization are tabulated in Table 1. The patient was discharged from the hospital after recovery, and chronic urticaria was continued to be managed with antihistaminics.

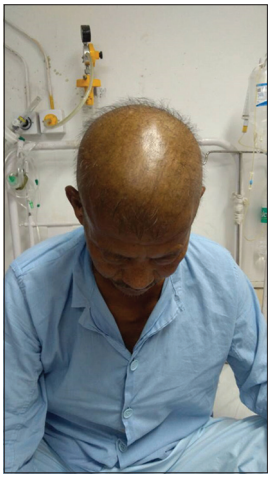

Figure 1: Clinical image of the patient showing alopecia

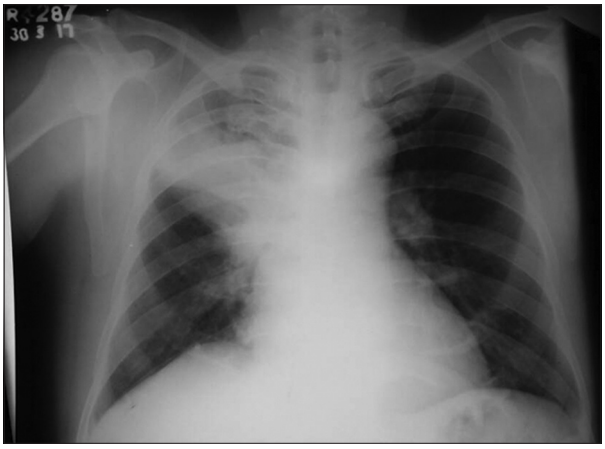

Figure 2: X ray chest PA View depicting lobar pneumonia

DISCUSSION

Azathioprine is a prodrug of 6-mercaptopurine (6-MP) synthesized by attaching an imidazole ring to the sulphur atom at the 6th position of the 6-MP molecule [4]. Since its inception in the year 1962, this drug has been widely used in dermatology, oncology, gastroenterology, and rheumatology for its antileukemic, anti-inflammatory, and immunosuppressive properties [5]. Despite its therapeutic benefits, 15–28% of patients treated with azathioprine have adverse drug reactions, which require dose reduction or withdrawal of the therapy [6].

After oral administration, azathioprine is absorbed almost completely by the gut. It is then converted non-enzymatically to 6-MP and then undergoes complex metabolism by three competitive enzymes. 6-MP is either oxidized by xanthine oxidase (XO) to 6-thiouric acid, methylated by thiopurine methyl transferase (TPMT) to form 6-methyl-mercaptopurine, or converted to 6-thioguanine nucleotides (6-TGN) by hypoxanthine guanine phosphoribosyl transferase (HGPRT) [7]. The relative activities of XO, HGPRT, and TPMT determine the net concentration of the active 6-TGN, which is responsible for the majority of azathioprine's efficacy and adverse effects [8].

TPMT activity in the red blood cell and other human tissues is regulated by genetic polymorphism. The frequency distribution of TPMT activity in human populations is trimodal: approximately 89% of the population have high enzyme activity and are homozygous for the wild-type allele (TPMTH), 11% inherit intermediate levels of enzyme activity with one wild-type and one variant allele (heterozygous TPMTH/TPMTL), while 1 in 300 subjects have no functional activity (two variant alleles, homozygous TPMTL) [9,10].

The adverse effects of thiopurines can be categorized into dose-dependent and dose-independent. Common dose-dependent effects are general malaise, nausea, vomiting, alopecia, diarrhoea, infectious complications, hepatitis, and myelosuppression. The latter includes rash, fever, arthralgia, myalgia, pancreatitis, and anaphylactic shock. Nausea and general malaise are the most frequently observed dose-dependent reactions [4,11,12].

It has been well recognized that those with low or absent TPMT enzyme activity are prone to developing rapid onset and severe myelotoxicity caused by intracellular 6-TGN accumulation [13]. Whereas, patients with high enzyme activity tend to metabolize 6-MP into 6-methyl mercaptopurine, which leads to hepatotoxicity [14]. The remaining adverse effects, such as influenza-like illness, intense myalgia, and pancreatitis, are thought to be related to the inosine triphosphate pyrophosphatase deficiency [15].

Currently, there are no standard guidelines for the management of azathioprine-induced myelosuppression.

Table 1: Laboratory investigations of the patient

Investigation parameters	Day 1	Day 3	Day 7	Day 15	Day 21	Day 30
Hemoglobin (g %)	12.4	7.6	7.8	8.1	9.2	10.6
Total leukocyte count (cells/Cumm)	450	660	610	1700	4,200	8,400
Platelet (cells/Cumm)	1.1 Lac	65,000	98,000	1,10,000	1,20,000	1,60,000
Urea (mg/dL)	24	81	82	71	68	54
Creatinine (mg/dL)	1.0	3	3.2	2.9	2.4	1.2

The major principles of management include treatment of febrile neutropenia with early commencement of empirical broad-spectrum antibiotics, prophylactic or therapeutic whole blood and platelet transfusion to maintain the physiological demand, and G-CSF administration for the recovery of leukocyte count after withdrawal of offending agent [16,17]. The dosage of G-CSF for adults is 5 μg/kg/day subcutaneously until the absolute neutrophil count reaches 2–3 × 10^3/μL [18].

CONCLUSION

Azathioprine is considered to be a safe immunomodulator, and adverse drug reactions are uncommon. This is an extremely rare presentation, as alopecia induced by azathioprine is dose-dependent and chronic. Clinicians using azathioprine could avert life-threatening toxicity by early recognition of cutaneous side effects such as alopecia.

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