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Case Report

A sudden shedding: azathioprine induced anagen effluvium

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ABSTRACT

Azathioprine is commonly used as immunosuppressive therapy for various autoimmune diseases including Takayasu arteritis. Myelosuppression is a recognized side effect of azathioprine, often requiring dose reduction. However, severe alopecia is rarely encountered. Here, a case of azathioprine-induced anagen effluvium and leucopenia that occurred in a 26-year-old woman with Takayasu arteritis who developed sudden diffuse non-scarring alopecia and leucopenia within three weeks of starting azathioprine therapy.

Keywords: Azathioprine, Leucopenia, Myelosuppression

INTRODUCTION

Azathioprine (AZA) is a purine analog and a cytotoxic pro-drug that gets converted to 6-mercaptopurine and interferes with purine metabolism, with adenine and guanine ribonucleotide production via suppression of inosinic acid synthesis thereby inhibiting the proliferation of rapidly dividing cells such as lymphocytes.[1] Although AZA is generally well tolerated, the most common adverse effects include nausea, vomiting, malaise, and myelosuppression. Less frequent adverse events are hepatotoxicity, pancreatitis, and alopecia.[2] Approximately 5–25% of patients on AZA therapy experience side effects, with severe myelosuppression potentially leading to life-threatening infections.[3]

Myelosuppression is both dose-dependent and idiosyncratic and can occur even at standard doses, particularly in individuals with genetic polymorphisms affecting azathioprine metabolism. Deficiency of thiopurine methyltransferase (TPMT) or nucleoside diphosphate–linked moiety X-type motif 15 (NUDT15) enzyme has been implicated as a significant risk factor for azathioprine toxicity, resulting in bone marrow suppression and alopecia. However, cases of myelosuppression and alopecia have also been reported in individuals with normal TPMT activity, suggesting other contributing mechanisms.[4]

CASE REPORT

A 26-year-old female, diagnosed case of Takayasu arteritis (type 3 disease), previously treated with nine doses of infliximab and maintained on mycophenolate mofetil (MMF) and methotrexate (MTX), presented with sudden onset of diffuse hair loss. In view of planned conception and stable disease status, her immunosuppressive therapy was switched from MMF and MTX to azathioprine (AZA) 50 mg/day. Within three weeks of initiating AZA, she reported abrupt shedding of large tufts of hair while combing (Figure 1).

Over the next few days, hair loss was progressive, developed extensive diffuse, non-scarring alopecia involving more than 75% of the scalp (Figures 2 and 3). On evaluation, she was found to have significant leucopenia with a total leukocyte count (TLC) of 2710/mm^3. Azathioprine was immediately discontinued in view of suspected drug-induced toxicity. Serial hematological monitoring showed progressive

improvement in TLC following azathioprine withdrawal (Figure 4). By day 7 after stopping AZA, her TLC increased to 4110/mm^3, indicating recovery of bone marrow suppression. Further evaluation revealed normal thiopurine methyltransferase (TPMT) activity, ruling out genetic predisposition to azathioprine toxicity. The patient was counseled regarding postponement of conception and was restarted on her previous regimen of MMF and MTX for maintenance of disease remission.

Figure 1: Sudden shedding of large tufts of hair collected after combing, reflecting abrupt onset diffuse hair loss.

Figure 2: Top view of the scalp showing diffuse, non-scarring alopecia with marked thinning and preservation of follicular openings, consistent with anagen effluvium.

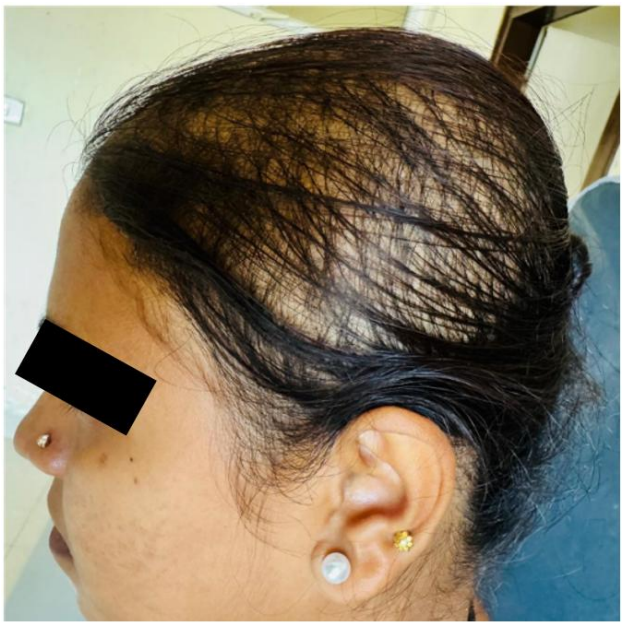

Figure 3: Lateral view of the scalp demonstrating diffuse hair loss with visible scalp.

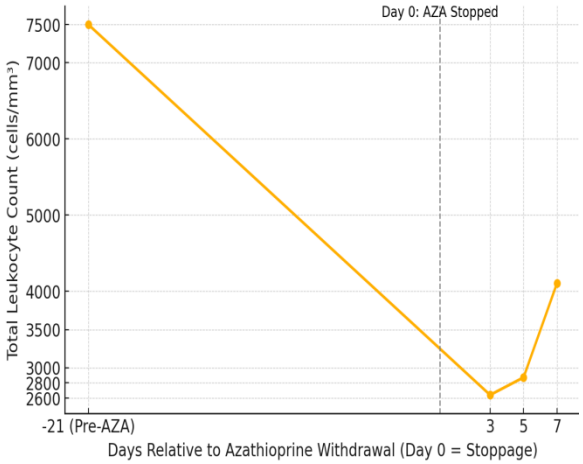

Figure 4: Trend of TLC before and after AZA withdrawal.

DISCUSSION

AZA is a purine analog prodrug that is widely used as an immunosuppressive agent in various autoimmune and inflammatory diseases. AZA is converted non-enzymatically to 6-mercaptopurine (6-MP), which undergoes metabolism by three major pathways: xanthine oxidase, thiopurine methyltransferase (TPMT), and hypoxanthine-guanine phosphoribosyltransferase (HGPRT). TPMT plays a key role in preventing the accumulation of cytotoxic thioguanine nucleotides (6-TGN) by methylating 6-MP into inactive metabolites. Myelosuppression is a well-documented dose-dependent and idiosyncratic adverse effect of AZA. Genetic polymorphisms in TPMT contributes to thiopurine toxicity. The prevalence of TPMT mutations in India

ranges from 1.2–10%. In 2014, a novel mutation in nucleoside diphosphate–linked moiety X-type motif 15 (NUDT15) was identified as another significant contributor to azathioprine-induced toxicity. The incidence of NUDT15 variants in the Indian population has been reported to be between 8.5–16%.[5] NUDT15 deficiency, more prevalent in East Asian populations, leads to the incorporation of active thioguanine metabolites into DNA, causing cell death in rapidly dividing cells, such as hematopoietic precursors and hair matrix keratinocytes.[6] This mechanism explains the association between myelosuppression and non-scarring alopecia in susceptible individuals. In South Asians, azathioprine toxicity is classically attributed to TPMT deficiency.

In the patient, TPMT levels were normal, and testing for NUDT15 polymorphisms could not be performed. Despite normal TPMT activity, she developed severe leucopenia and anagen effluvium within three weeks of starting azathioprine at 50 mg/day. These adverse effects resolved following immediate withdrawal of the drug and supportive care. Similar observations have been reported in earlier case studies, suggesting that factors other than TPMT deficiency, such as NUDT15 variants, may play a significant role.

Kim et al reported a case of azathioprine-induced alopecia and myelosuppression occurring within 28–42 days of therapy, while Bhokare et al described a patient with vitiligo developing similar adverse effects within 15 days of starting azathioprine.[7,8] In a series from China, five cases of alopecia with leukopenia were reported, and three patients were heterozygous for TPMT mutations while two were homozygous.[9] The role of NUDT15 mutations was emphasized by Lee et al who found all NUDT15 homozygous patients developing severe leukopenia and alopecia.[10]

Given the widespread use of azathioprine and the availability of genotyping assays, TPMT and NUDT15 testing prior to initiation of therapy may help identify patients at risk for severe toxicity. However, in resource-limited settings, close clinical monitoring and serial leukocyte counts remain practical tools for early detection of myelotoxicity. Unusual hair loss in patients receiving azathioprine should prompt clinicians to suspect impending myelosuppression and consider drug withdrawal.

This case reinforces the importance of recognizing alopecia as a potential early clinical marker of azathioprine toxicity. Prompt identification and discontinuation of the offending agent can lead to recovery of bone marrow function and hair regrowth.

CONCLUSION

AZA-induced anagen effluvium is a rare but important early clinical marker of impending bone marrow suppression. Sudden diffuse hair loss in patients on azathioprine should alert clinicians to possible myelotoxicity and prompt immediate hematological evaluation. TPMT and NUDT15 testing, though helpful in identifying susceptible individuals, cannot be performed in all patients before azathioprine initiation due to limited availability and high cost in many centres. Normal TPMT levels do not eliminate the risk of myelosuppression, as other genetic factors such as NUDT15 variants may contribute.

This report highlights the importance of recognizing alopecia as an external clinical clue to underlying bone marrow suppression. The patients on azathioprine therapy should be evaluated for acute hair loss, which may serve as a surrogate marker of impending myelotoxicity, and subsequently undergo blood count monitoring to prevent severe drug-induced complications.

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