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Research Article

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Drug Induced Myelosuppression and Alopecia Totalis in Ulcerative Colitis Patient: Unmasking the Enigma

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ABSTRACT

Azathioprine and Sulfasalazine are common drugs used in various conditions including inflammatory bowel disease (IBD) to induce remission and control the disease. The common side effects reported are headache, gastrointestinal symptoms, pancreatitis and myelosuppression are with the use of both drugs. Significant pancytopenia associated with azathioprine use in patients with Thiopurine methyltransferase or NUDT15 mutations.

We report a case of severe pancytopenia and myelosuppression following treatment with sulfasalazine and Azathioprine in a patient with ulcerative colitis. Pancytopenia attributed to drugs combination in a setting of normal enzyme testing may hint to a drug interaction potentiating their side effect and toxicity.

Keywords: Inflammatory Bowel Disease, Ulcerative Colitis, Azathioprine, Sulfasalazine, Pancytopenia, Myelosuppression, Bone Marrow Suppression, Leukopenia

Background

Inflammatory bowel disease (IBD), including ulcerative colitis and Crohn's disease, comprises chronic immune-mediated disorders associated with significant morbidity [1]. The incidence of pediatric IBD is increasing worldwide, with approximately 25% of patients being diagnosed before the age of 20 years [2]. Various medications are used for both induction and maintenance of remission, including 5-aminosalicylic acid (5-ASA) derivatives and immunomodulators.

Azathioprine is a purine analogue that exerts its therapeutic effect by interfering with DNA synthesis. It is a prodrug that is metabolized into active 6-thioguanine nucleotides (6-TGN) through the thiopurine metabolic pathway [3]. Common adverse effects include nausea, vomiting, and myelosuppression resulting from increased cytotoxic metabolite concentrations [4]. Less common but potentially serious adverse effects include hepatotoxicity and pancreatitis [5]. Thiopurine methyltransferase (TPMT) is a key enzyme involved in azathioprine metabolism, and its activity is inversely correlated with 6-TGN levels. Numerous cases of severe myelosuppression have been associated with reduced TPMT activity. In addition, mutations in the NUDT15 gene have been linked to azathioprine-induced bone marrow suppression [6,7]. Reversible alopecia has also been reported in patients receiving therapeutic doses despite normal TPMT activity.

Sulfasalazine is an effective treatment, particularly for patients with ulcerative colitis. Reversible myelosuppression has been reported following initiation of this medication, while bone marrow necrosis has been described rarely [8]. We report a case of severe azathioprine-induced myelosuppression accompanied by alopecia in a patient with ulcerative colitis with normal TPMT activity and negative NUDT15 gene mutation.

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Case Presentation

An 11-year-old girl with a history of psoriasis and moderate left-sided ulcerative colitis presented to our institution. Her family history was significant for psoriasis in her older brother and hypothyroidism in her mother. She was initially treated with sulfasalazine 500 mg three times daily (51 mg/kg/day). At the 3-week follow-up, she had not achieved full remission, with a Pediatric Ulcerative Colitis Activity Index (PUCAI) score of 40. Thiopurine methyltransferase (TPMT) activity was normal at 17.3 U/mL RBC; therefore, azathioprine (AZA) was initiated at a dose of 1.7 mg/kg/day. However, she did not undergo the recommended laboratory monitoring because of financial constraints.

The patient initially responded well to treatment, with near-complete resolution of gastrointestinal symptoms during the first month and a PUCAI score of 10. One month after starting azathioprine, she presented with an episode of hematemesis and significant hair loss that had progressed over several days. She had no fever or other clinical signs of infection. Physical examination revealed alopecia totalis (Figure 1) and a bruise on her left leg, without lymphadenopathy, hepatosplenomegaly, petechiae, or mucosal bleeding.

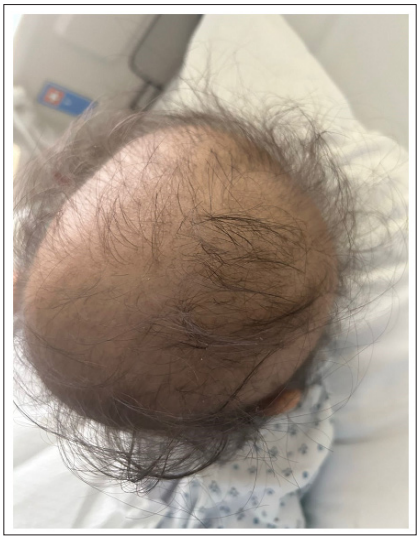
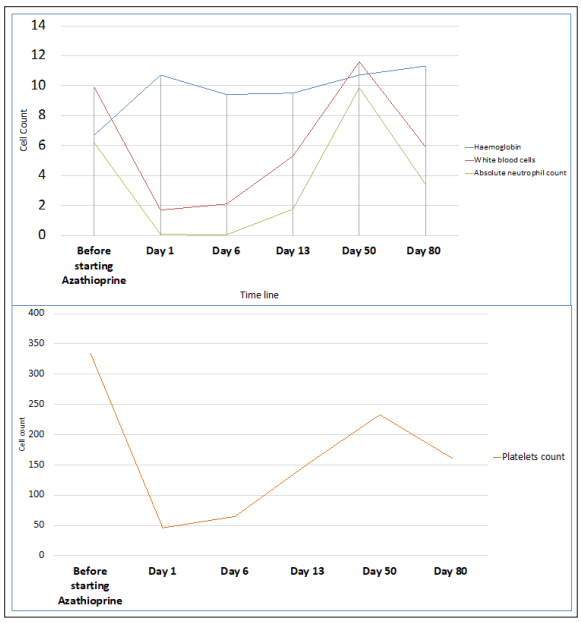


Figure 1: Hair loss in our patient

Laboratory investigations demonstrated pancytopenia, with a hemoglobin level of 10.7 g/dL (reference range: 11.5–15.5 g/dL), platelet count of 46 × 10^3/µL (170–450 × 10^3/µL), white blood cell count of 1.7 × 10^3/µL (5.0–13.0 × 10^3/µL), and an absolute neutrophil count (ANC) of 70/µL (2.0–8.0 × 10^3/µL), as shown in Table 1. Extensive investigations, including viral studies, blood cultures, peripheral blood film, and autoimmune screening, were unremarkable. Given the suspicion of drug-induced myelosuppression, azathioprine was discontinued, and empirical antibiotic therapy was initiated.

The hematology team was consulted and supported the diagnosis of medication-induced bone marrow suppression, recommending bone marrow examination only if blood counts failed to improve. Despite discontinuation of azathioprine, the ANC continued to decline, prompting administration of a single 3 mg dose of pegfilgrastim. Subsequently, the patient developed fever, and a repeat septic workup was performed, which remained negative. Antibiotic therapy was escalated to piperacillin-tazobactam.



Graph 1: Trend of Blood Cell Counts in our Patient

Table 1: blood cell counts through the course of management.

Component	Normal range	Before starting Azathioprine	Day 1	Day 6	Day 13	Day 50 – discharge	Day 80 – follow-up
Haemoglobin	11–14 g/dL	6.7	10.7	9.4	9.5	10.7	11.3
White blood cells	5.0–15.0 ×10^9/L	9.9	1.7	2.1	5.3	11.6	5.9
Absolute neutrophil count	2.0–8.0 ×10^3/µL	6.2	0.07	0.06	1.76	9.87	3.41
Platelets count	200–490 ×10^9/L	335	46	65	151	233	161

Following treatment, her blood counts gradually improved. At discharge after 10 days, her hemoglobin was 9.5 g/dL (reference range: 11.5–15.5 g/dL), platelet count was 151 × 10^3/µL (170–450 × 10^3/µL), white blood cell count was 5.3 × 10^3/µL (5.0–13.0 × 10^3/µL), and ANC was 1,760/µL (2.0–8.0 × 10^3/µL). Her recovery was spontaneous, and no additional doses of pegfilgrastim were required. Bone marrow biopsy was deferred because of the steady improvement in blood counts.

Measurement of 6-thioguanine nucleotide levels showed a concentration of 157 pmol/8 × 10^8 red blood cells (therapeutic range: 235–450 pmol/8 × 10^8 red blood cells). Genetic testing revealed no polymorphisms in either the TPMT or NUDT15 genes. At follow-up 2 weeks after discharge, her hair had begun to regrow normally. Although she reported intermittent blood in the stool, her laboratory

parameters continued to improve. She was subsequently started on oral and rectal mesalazine, with a good clinical response.

Discussion

Azathioprine is a prodrug that undergoes complex metabolism to generate its active metabolites. Following administration, approximately half of the ingested drug is excreted unchanged in the urine, while a substantial proportion of the remainder is protein-bound [9]. Only about 25% of the administered dose is converted to 6-mercaptopurine (6-MP) through the action of glutathione in erythrocytes. Several metabolic pathways are involved in the subsequent metabolism of 6-MP. Xanthine oxidase catalyzes its conversion to the inactive metabolite 6-thiouric acid. Alternatively, 6-MP is metabolized through the actions of thiopurine S-methyltransferase (TPMT) and hypoxanthine-guanine phosphoribosyltransferase (HGPRT) to form metabolites including 6-methylmercaptopurine (6-MMP) and 6-thioguanine nucleotides (6-TGN). The active metabolite thioguanosine triphosphate (TGTP) is subsequently converted by nucleoside diphosphate-linked moiety X-type motif 15 (NUDT15) to the inactive metabolite thioguanosine monophosphate (TGMP). Deficiencies or functional abnormalities in TPMT and NUDT15 increase the risk of azathioprine toxicity because of impaired thioguanine metabolism and accumulation of active metabolites [10].

The principal dose-dependent adverse effect of azathioprine is bone marrow suppression. This most commonly manifests as leukopenia, although pancytopenia may occur in more severe cases. Dose reduction is generally recommended when the white blood cell count falls below $3.0 \times 10^3/\mu L$, severe neutropenia develops (ANC <1,000/μL), or significant lymphopenia occurs (lymphocyte count <600/μL). Severe myelosuppression is more frequently observed in patients with TPMT or NUDT15 deficiencies or in the presence of drug interactions that alter thiopurine metabolism [11]. Alopecia is another recognized adverse effect and may occur despite therapeutic dosing and normal TPMT and NUDT15 test results.

As the active metabolites of azathioprine are intracellular, serum azathioprine concentrations are poor indicators of therapeutic efficacy and toxicity. Therefore, treatment should be initiated at a low dose and titrated gradually. Complete blood counts should be monitored every two weeks during dose escalation and every four to six weeks once a stable dose has been achieved. Because leukopenia may result from causes unrelated to thiopurine toxicity, erythrocyte 6-thioguanine nucleotide (6-TGN) concentrations may provide a more reliable indicator of drug exposure and treatment adherence [12,13]. However, metabolite monitoring alone has limited ability to predict adverse effects. Genetic and functional testing for TPMT and NUDT15 are available to identify patients at increased risk of thiopurine toxicity. Dosing recommendations for individuals with reduced enzyme activity have been published by the Clinical Pharmacogenetics Implementation Consortium (CPIC) and the Dutch Pharmacogenetics Working Group (DPWG) [14]. Nevertheless, there is currently no universal consensus regarding routine pre-treatment screening. Although homozygous variants are uncommon in the general population, they are disproportionately represented among patients who develop severe thiopurine-induced myelosuppression. Notably, NUDT15 variants are more prevalent in Asian populations, whereas TPMT deficiency is less common in these groups.

In our patient, pancytopenia developed approximately 30 days after initiation of azathioprine, which is consistent with previous reports describing onset between 10 and 60 days after treatment initiation. However, myelosuppression may also occur months or even years after starting therapy [15]. Previous studies have reported azathioprine-associated myelosuppression across a wide dose range of 1.5–3 mg/kg/day. Recovery times vary from several weeks to months and may be influenced by the use of granulocyte colony-stimulating factor (G-CSF) [16]. In our case, neutropenia resolved within 10 days following discontinuation of azathioprine and administration of pegfilgrastim.

Sulfasalazine may also cause bone marrow suppression, although this adverse effect is uncommon. Following oral administration, approximately 25% of the drug is absorbed in the small intestine. The remainder is metabolized by colonic bacteria into sulfapyridine and 5-aminosalicylic acid (5-ASA). Sulfapyridine is systemically absorbed and is primarily responsible for most adverse effects, whereas 5-ASA exerts its therapeutic effect locally within the colonic mucosa [17]. Bone marrow suppression has been reported with both sulfasalazine and 5-ASA therapy. Although the condition is usually reversible following drug discontinuation, rare cases of bone marrow necrosis have been described [18]. Therefore, prompt discontinuation is warranted in patients who develop cytopenia, unexplained fever, or sore throat after initiation of therapy.

Conclusion

Both Azathioprine and Sulfasalazine are effective drugs used in the treatment of IBD. Bone marrow suppression is a known side effects for both drugs. Although it can be mild, and self-limited, some severe cytopenia can be seen. This warrants cell counts monitoring and dose reduction or discontinuation of the drug. Testing for enzyme deficiency can be helpful to identify patients who are at risk. However, normal testing does not exclude the possibility of drug-related bone marrow suppression.

Consent for Publication

Informed and written consent taken from parents for publication of the details of their child's medical case and any accompanying images.

Competing interests

The authors have no conflicts of interest to declare.

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Authors' contributions

Sabsabee M: writing the case summary, writing the initial manuscript draft.

Almheiri M: management of the patient, conceptualized the study, and edited the final manuscript, literature review.

E.M Management of the patient, provided critical manuscript review and expert input.

Madasu A: management of the patient, conceptualize the topic,

provided critical manuscript review and expert input.

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