RESEARCH PAPER

Azathioprine-Induced Idiosyncratic Bone Marrow Suppression And Neutropenic Sepsis In Patients With Bullous Pemphigoid: A Case Series

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Abstract
Azathioprine (AZA) is a commonly used adjuvant immunosuppressant in autoimmune blistering diseases. While dose-dependent myelotoxicity is a known side effect of AZA, idiosyncratic reactions may also occur, causing life-threatening bone marrow suppression. Here, we present a case series of elderly female patients with bullous pemphigoid who developed severe azathioprine-induced myelotoxicity, including neutropenic sepsis and alopecia, following initiation of azathioprine therapy. One patient had normal thiopurine methyltransferase (TPMT) activity, while the other demonstrated intermediate TPMT activity, highlighting that life-threatening azathioprine toxicity may occur despite normal enzyme activity. Timely drug withdrawal, prompt infection control, and hematopoietic growth factor support resulted in favorable clinical outcomes.

Keywords: Azathioprine; Bone marrow suppression; Bullous pemphigoid; Myelotoxicity; Thiopurine methyltransferase
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Introduction

Bullous pemphigoid (BP) is a chronic autoimmune blistering disorder, most commonly treated with systemic corticosteroids. To reduce long-term steroid-related side effects, steroid-sparing immunosuppressive agents such as azathioprine (AZA) are often used(1). AZA is metabolized in the liver to 6-mercaptopurine, which is further converted into cytotoxic thioguanine nucleotides. The activity of these metabolites is controlled by the enzymes thiopurine methyltransferase (TPMT) and nudix hydrolase 15 (NUDT15). Reduced enzyme activity can lead to excessive drug buildup, increasing the risk of severe bone marrow suppression(2). Although rare, AZA-induced hematologic toxicity can lead to life-threatening sepsis, even at standard therapeutic doses(3).

Case 1

A 68-year-old woman with bullous pemphigoid was started on azathioprine (AZA) as a steroid-sparing treatment. After two days, she developed alopecia and painful oral ulcers. However, due to limited healthcare access and awareness in her rural area, she was unaware of potential side effects and continued the medication despite these warning signs. By day ten, she presented with fever, malaise, anorexia, and painful perineal swelling. On admission, she was febrile and appeared ill, with a fluctuant, tender perineal abscess. Laboratory tests showed pancytopenia with a significantly low reticulocyte count. A peripheral smear revealed moderate microcytic hypochromic anemia, leucopenia with lymphocytic preponderance and reactive lymphocytes, and mild thrombocytopenia. Chest X-ray and abdominal ultrasound were normal, while pus culture from the abscess grew Pseudomonas aeruginosa. Suspecting idiosyncratic AZA-induced severe bone marrow suppression with neutropenic sepsis, the AZA was immediately discontinued. The patient was treated with intravenous meropenem based on sensitivity testing, daily granulocyte–macrophage colony-stimulating factor (GM-CSF), romiplostim (a thrombopoietin receptor agonist), and surgical incision and drainage of the abscess. Recovery from severe neutropenia took ten days of GM-CSF therapy, and she received two doses of romiplostim followed by a week of eltrombopag (TPO-RA). She gradually improved and was discharged on the seventh hospital day with instructions to continue GM-CSF for three more days and complete a seven-day course of oral antibiotics. On follow-up on day 10 after discharge, her complete blood counts had normalized; oral ulcers resolved within two weeks; and alopecia gradually subsided over six months. Enzyme testing later showed TPMT activity of 13 U/mL (reference: 15–26 U/mL), indicating intermediate enzyme function (Table 1) (Figure 1).

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Case 2

A 62-year-old woman with Bullous pemphigoid was initiated on azathioprine (AZA) as a steroid-sparing agent following prolonged systemic corticosteroid therapy. She had no prior history of cytopenias or drug hypersensitivity. Baseline complete blood counts and liver function tests were within normal limits. Thiopurine methyltransferase (TPMT) activity was assessed before initiation of azathioprine and found to be normal (16 U/mL; reference range 15–26 U/mL).

After 14 days of therapy, she developed oral ulcers, diffuse hair fall, and low-grade fever, which were initially attributed to intercurrent infection. She continued AZA until day 24, when she presented with high-grade fever, profound generalised weakness, and odynophagia.

On examination, she was febrile and toxic-looking with extensive oral ulcers and no focal source of infection. Laboratory evaluation revealed severe pancytopenia with markedly reduced reticulocyte counts. Peripheral smear showed normocytic normochromic anemia, severe leukopenia without blasts, and thrombocytopenia. Blood cultures were sterile, and imaging studies were unremarkable.

A diagnosis of idiosyncratic azathioprine-induced bone marrow suppression with febrile neutropenia was made. Azathioprine was immediately discontinued, and the patient received empirical broad-spectrum intravenous antibiotics along with daily granulocyte–macrophage colony-stimulating factor (GM-CSF) and eltrombopag, each administered for five days. She demonstrated gradual hematological recovery over eight days, with complete resolution of fever and mucositis. Thiopurine methyltransferase (TPMT) activity had been within the reference range on pre-treatment testing and on repeat assessment was at the upper-normal range (25 U/mL; reference range 15–26 U/mL), supporting a non–non-TPMT-mediated mechanism of azathioprine toxicity. Although NUDT15 genotyping was not performed, the contribution of other pharmacogenetic factors, including nudix hydrolase 15 (NUDT15), cannot be excluded. Following discharge, hematological parameters normalized within two weeks, and alopecia showed gradual improvement over the ensuing months (Table 1) (Table 2) (Figure 2).

Case 3

A 70-year-old woman with bullous pemphigoid was initiated on azathioprine as a steroid-sparing agent at an outside hospital. Thiopurine methyltransferase (TPMT) testing was not performed before initiation, and baseline complete blood counts were within normal limits.

Within one week, she developed oral ulcers and hair loss, but continued the medication as she did not recognize these symptoms as drug-related. On day nine, she presented to the OPD of our hospital with fever, malaise, and anorexia. She was febrile and clinically unwell on examination.

Laboratory investigations revealed severe pancytopenia with a markedly reduced reticulocyte count. Peripheral blood smear demonstrated microcytic hypochromic anemia, leukopenia with reactive lymphocytes, and thrombocytopenia. Microbiological cultures showed no growth. Chest radiography and abdominal ultrasonography were unremarkable.

A diagnosis of azathioprine-induced severe bone marrow suppression complicated by neutropenic sepsis was made, and azathioprine was immediately discontinued. The patient was treated with empirical intravenous antibiotics, along with daily granulocyte-macrophage colony-stimulating factor (GM-CSF). Due to persistent thrombocytopenia, romiplostim was administered, followed by a short course of eltrombopag. Supportive care was continued.

Hematological recovery required ten days of GM-CSF therapy. At follow-up, complete blood counts had normalized, oral ulcers resolved within two weeks, and alopecia gradually improved over the subsequent months. TPMT enzyme assay revealed intermediate activity (13 U/mL; reference range 15–26 U/mL), consistent with increased susceptibility to thiopurine-induced toxicity. The patient and caregivers were provided with detailed counseling regarding azathioprine-related adverse effects, the importance of early symptom recognition, and the need for regular haematological monitoring to prevent recurrence (Table 1) (Table 2).

Discussion

This case series underscores the critical importance of early recognition of idiosyncratic azathioprine (AZA) toxicity. Although AZA remains a widely used steroid-sparing agent in autoimmune diseases, severe haematological toxicity may occur even at therapeutic doses(4). The risk of myelosuppression is determined by individual variation in thiopurine metabolism, particularly the activity of thiopurine methyltransferase (TPMT) and nudix hydrolase 15 (NUDT15) enzymes. Reduced activity of either enzyme predisposes to toxic accumulation of 6-thioguanine nucleotides (6-TGNs), the active metabolites responsible for both immunosuppression and marrow toxicity(5).

AZA is a prodrug that is rapidly converted into 6-mercaptopurine (6-MP). From this point, metabolism proceeds through competing activation and inactivation pathways. In the activation pathway, 6-MP is converted into 6-TGNs, which incorporate into DNA and RNA to exert immunosuppressive effects. Excessive accumulation, however, disrupts normal hematopoiesis and leads to bone marrow suppression(3,5).

The detoxification pathways are mediated primarily by TPMT and NUDT15. TPMT catalyzes the S-methylation of 6-MP and its metabolites into inactive derivatives. Patients with complete TPMT deficiency are at risk of life-threatening pancytopenia even with standard doses, while those with heterozygous or intermediate activity are prone to severe myelosuppression if doses are not appropriately adjusted (1–3% of Asians carry TPMT variant alleles)(6). NUDT15, in contrast, hydrolyzes active thioguanine

triphosphates into less toxic monophosphates. Loss-of-function variants abolish this protective step, resulting in direct accumulation of cytotoxic metabolites in hematopoietic stem cells. Importantly, NUDT15 variants are especially prevalent in Asian populations (≈10–15% heterozygotes, 1–2% homozygotes), making genetic testing highly relevant in this demographic(7).

Another clinical challenge is the persistence of toxic metabolites. Although AZA itself has a short plasma half-life (~5 hours) and 6-MP is cleared within about an hour, 6-TGNs stay in red blood cells and bone marrow for 3–5 days. As a result, even after stopping AZA, toxic metabolites may remain at harmful levels for 1–2 weeks, with cytopenias often reaching their lowest point several days after stopping. Hematological recovery usually takes 2–4 weeks and can be delayed further in the presence of genetic deficiencies, renal dysfunction, or severe marrow injury(4).

In this case series, intermediate and normal TPMT activity has precipitated severe bone marrow suppression, highlighting that even partial enzyme deficiency, rarely normal TPMT may be clinically significant(8). Early warning signs such as alopecia and painful oral ulcers, both evident in this case, may precede hematological deterioration and should prompt immediate drug discontinuation and urgent hematological evaluation(9).

Where pharmacogenetic testing is not readily available, frequent monitoring of complete blood counts during the first weeks of therapy remains the most practical safeguard. This case series, therefore, reinforces the need to integrate pharmacogenetic screening, vigilant clinical observation, and regular hematological monitoring to minimize the risk of serious AZA-induced complications(4).

Conclusion

This case series highlights the critical importance of integrating pharmacogenetic testing, vigilant clinical surveillance, and timely therapeutic intervention in optimizing the safety of azathioprine therapy. Pretreatment evaluation of TPMT and NUDT15 activity, wherever feasible, serves as a valuable tool to guide dosing and identify patients predisposed to life-threatening hematologic toxicity. In regions where pharmacogenetic facilities are limited, careful monitoring of complete blood counts during the initial weeks of treatment becomes indispensable. Equally important is the early recognition of sentinel clinical warning signs-such as alopecia and severe oral ulceration-which should immediately raise suspicion of drug-induced marrow suppression. Once toxicity is suspected, prompt discontinuation of azathioprine, combined with the judicious use of hematopoietic growth factors, thrombopoietin receptor agonists, and targeted antimicrobial therapy, can substantially mitigate morbidity and mortality. By integrating genetic evaluation, close clinical monitoring, and individualized therapeutic strategies, this case series highlights the indispensable role of clinician awareness in averting and managing serious azathioprine-related complications.

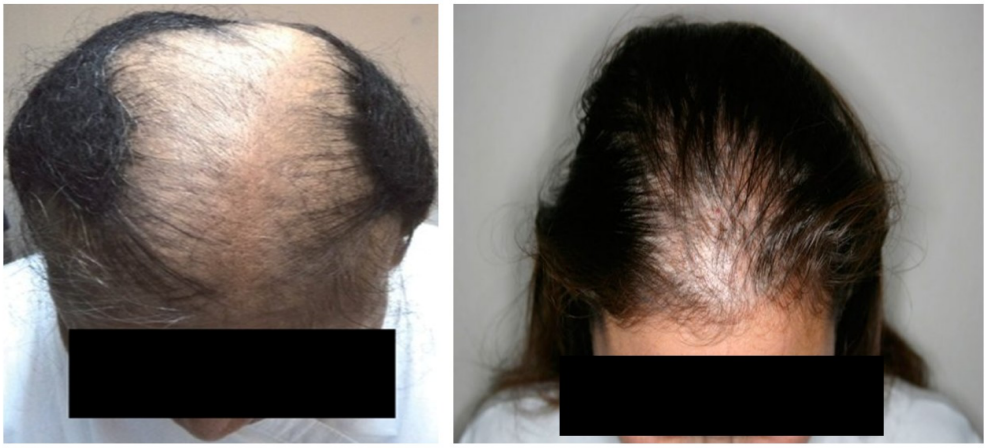

Figure 1: Before-and-after images showing azathioprine-induced hair loss at onset (left) and clinical improvement after three months (right).

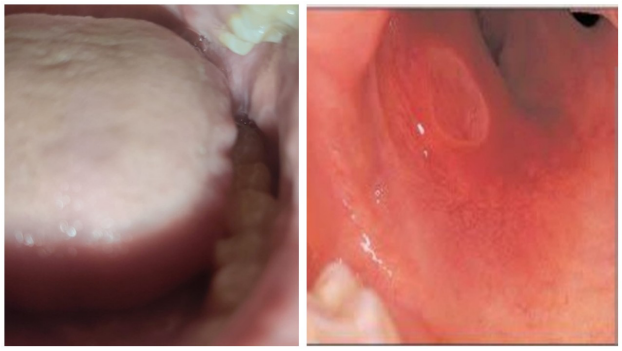

Figure 2: Oral mucosal changes associated with pancytopenia, showing diffuse pallor of the tongue (left) and painful aphthous-like ulceration with surrounding erythema suggestive of neutropenia-related mucositis (right).

Table 1: Temporal changes in hematological parameters over the first 7 Days among the three cases.

Hematology & Blood Counts						
Parameter	**Cases**	**Day 1**	**Day 3**	**Day 5**	**Day 7**	**Reference Range (Approx.)**
White Blood Cell (WBC) Count (mm^{-3})	Case 1	490	740	940	1380	4,000-11,000
	Case 2	520	780	980	1450	
	Case 3	540	820	1020	1520	
Neutrophil (%)	Case 1	16.40	6.70	14.90	50	40-70
	Case 2	15.8	7.2	16.1	48.6	
	Case 3	14.6	8.1	15.4	47.2	
Eosinophil (%)	Case 1	6.10	9.50	1.10	0.70	1-6
	Case 2	5.8	8.9	1.4	0.9	
	Case 3	6.2	8.1	1.6	1.0	
Basophil (%)	Case 1	0	0	0	0.70	0-1
	Case 2	0	0	0.2	0.8	
	Case 3	0	0	0.3	0.9	
Lymphocyte (%)	Case 1	75.50	82.40	81.90	44.20	20-40
	Case 2	76.2	81.6	80.5	45.1	
	Case 3	76	80.8	80.2	46	
Monocytes (%)	Case 1	2.00	1.40	1.10	2.2	2-8
	Case 2	2.2	1.8	1.8	2.6	
	Case 3	3.2	3	2.5	4.9	
Reticulocyte Count (%)	Case 1	0.31	-	-	-	0.5-2.5
	Case 2	0.35	-	-	-	
	Case 3	0.38	-	-	-	
Hemoglobin (g/dl)	Case 1	7.6	8.2	7.9	10.90	12-16 (F) / 13-17 (M)
	Case 2	7.8	8.4	8.1	11.1	
	Case 3	7.9	8.6	8.2	11.3	
Platelet Count (mm^{-3})	Case 1	7.8×10^4	10×10^4	7.5×10^4	8.6×10^4	$15\text{-}45 \times 10^4$
	Case 2	8.2×10^4	10.6×10^4	10.8×10^4	11.1×10^4	
	Case 3	6.5×10^4	10.2×10^4	8.1×10^4	9.4×10^4	

Table 2: Biochemical investigations and ancillary laboratory findings

Parameters	**Values**			**Reference Range (Approx.)**
	Case 1	**Case 2**	**Case 3**	
Kidney Function Test				
Blood Urea Nitrogen (BUN)	12	14	15	7-20 mg/dl
Creatinine	0.8 l	0.6	0.9	0.6-1.3 mg/dl
Liver Function Test				

Total Protein	6.2	6.1	6.0	6.0-8.3 g/dl
Albumin	3.5	3.8	3.6	3.5-5.0 g/dl
Total Bilirubin	0.97	0.7	0.68	0.1-1.2 mg/dl
Aspartate Aminotransferase (AST)	34	17	14	10-40 U/L
Alanine Aminotransferase (ALT)	28	32	38	7-56 U/L
Alkaline Phosphatase (ALP)	65	62	63	40-130 U/L
Gamma-Glutamyl Transpeptidase (GGT)	21	30	32	9-48 U/L
Iron Profile Test				
Serum Iron	83	78	74	50-170 µg/dl
Total Iron Binding Capacity (TIBC)	189	250	245	240-450 µg/dl
% Transferrin Saturation	44	40	38	20-50%
Serum Ferritin	258	272	265	12-300 ng/ml
Other Tests				
Erythrocyte Sedimentation Rate (ESR)	99	74	70	<20 mm/hr (F) / <15 mm/hr (M)
Vitamin B12	239	246	252	200-900 pg/ml
Fever Profile	Negative (Dengue, Leptospirosis, Scrub Typhus, Malaria)	Negative (Dengue, Leptospirosis, Scrub Typhus, Malaria)	Negative (Dengue, Leptospirosis, Scrub Typhus, Malaria)	_

Disclosure

Conflict of interest: The authors declare no conflict of interest.

Patient Consent: Written informed consent was obtained from all patients for publication of their clinical information.

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