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Azathioprine-Induced Severe Myelosuppression Mimicking Disease Flare in Ulcerative Colitis: A Case Report

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ABSTRACT

Background: Azathioprine is widely used as a steroid-sparing immunomodulator in the long-term management of ulcerative colitis; however, early-onset myelotoxicity remains one of its most serious and potentially life-threatening complications. The clinical presentation of azathioprine-induced marrow suppression frequently overlaps with symptoms of active ulcerative colitis, creating substantial diagnostic uncertainty. Early recognition is critical, particularly given the influence of pharmacogenetic susceptibility—most notably TPMT and NUDT15 variants—on the development of abrupt and profound cytopenias.

Case Presentation: We report a 68-year-old man with ulcerative colitis who presented with progressive weakness, fatigue, and profuse bloody diarrhea one month after initiating azathioprine therapy. Initial laboratory testing revealed severe pancytopenia, prompting immediate discontinuation of the drug and initiation of supportive care. Despite withdrawal of azathioprine, cytopenias continued to worsen over the following 48–72 hours, reaching a nadir of 0.59×10^3/μL WBC and 27×10^3/μL platelets. Beginning on hospital day four, hematologic recovery became evident, with rapid normalization of cell counts by day six and complete clinical resolution at early outpatient follow-up. The temporal pattern of decline and subsequent brisk rebound strongly supported acute azathioprine-induced severe myelosuppression rather than an intrinsic hematologic disorder. The patient was transitioned to mesalamine maintenance therapy, and plans were made to initiate infliximab as a safer long-term immunomodulatory strategy.

Conclusion: This case illustrates the diagnostic challenges posed by early azathioprine-induced marrow toxicity, particularly when symptoms mimic an ulcerative colitis flare. The predictable delayed nadir of cytopenias and rapid recovery following drug withdrawal underscore the importance of timely hematologic monitoring during the initial weeks of thiopurine therapy. Early identification enables prompt cessation of the offending agent and prevents progression to catastrophic complications. Given the severity of toxicity observed, thiopurines should not be reintroduced, and biologic agents represent a safer alternative for long-term disease control.

Keywords: Azathioprine, Myelotoxicity, Pancytopenia, Ulcerative colitis, Drug-induced myelosuppression

Introduction

Azathioprine is a purine analog immunomodulator widely used in the long-term management of ulcerative colitis (UC), particularly for steroid-sparing maintenance therapy.[1-3] By inhibiting lymphocyte proliferation, it helps maintain remission and reduce the need for repeated corticosteroid courses.[1,2] Despite its proven efficacy, azathioprine is associated with a narrow therapeutic window and several potentially serious adverse effects.[2,4,5] Among these, hematologic toxicity—ranging from isolated leukopenia to severe pancytopenia and, in rare instanc-

es, life-threatening bone marrow aplasia—remains the most feared complication.[3,4,6,7] Reported rates of clinically significant myelotoxicity vary between 2% and 7%, but many studies suggest that the true incidence may be higher in real-world practice, particularly in populations with unrecognized genetic susceptibility.[3,5,8-10]

Myelotoxicity typically emerges during the first few weeks of therapy, often before steady-state thiopurine metabolites are reached.[4,11,12] Early toxicity is strongly associated with thiopurine methyltransferase (TPMT) and, more importantly in many Asian and Middle Eastern populations, nudix hydrolase 15 (NUDT15) polymorphisms.[10,12-15] However, severe marrow suppression can also occur in individuals without known enzymatic deficiencies, making clinical vigilance essential even when pre-treatment testing is unavailable or normal.[4,11,16,17]

A major diagnostic challenge arises because the early symptoms of myelotoxicity—such as fatigue, pallor, diarrhea, and mucosal bleeding—overlap substantially with those of active UC.[4,8,11,18] Moreover, gastrointestinal symptoms may persist or worsen despite cytopenias, misleading clinicians toward the assumption of an inflammatory flare.[4,8,11,18] Failure to recognize this overlap may result in inappropriate escalation of immunosuppression, delay in stopping the offending agent, and increased risk of sepsis or catastrophic bleeding.[4,11,17,19]

Here, we report a case of severe azathioprine-induced severe myelosuppression developing shortly after therapy initiation in a patient with ulcerative colitis. The presentation closely mimicked a disease flare, highlighting the importance of routine hematologic monitoring and careful clinical interpretation during the early phases of thiopurine therapy.

Case Presentation

A 68-year-old male with a known diagnosis of ulcerative colitis presented to the emergency department with progressive weakness, marked fatigue, and profuse bloody diarrhea occurring more than ten times daily. These symptoms had intensified over several days. His disease had recently been managed at an outside center, where colonoscopy reportedly demonstrated left-sided colonic involvement, and azathioprine (3×50 mg daily, 3 mg/kg/day in a thin, 50-kg patient) together with mesalamine (3×1600 mg daily) was initiated approximately one month before presentation in the setting of an acute disease flare. Detailed records regarding prior treatment responses were not fully available at the time of admission. His corticosteroid regimen had been discontinued around the same time, although the exact treatment sequence at the outside center could not be fully reconstructed. He denied fever, chills, or systemic symptoms suggestive of overt infection. His medical history included cardiovascular comorbidities for which he was taking clopidogrel.

On arrival, the patient appeared pale, lethargic, and volume depleted but remained hemodynamically stable. Abdominal evaluation revealed mild left lower quadrant tenderness without guarding or rebound. Initial laboratory evaluation demonstrated severe pancytopenia, with a white blood cell (WBC) count of 1.08×10^3/μL, hemoglobin 6.7 g/dL, and platelets 45×10^3/μL. Red blood cell indices showed normocytic, normochromic anemia consistent with acute blood-loss anemia compounded by marrow suppression. CRP was mildly elevated at 5.7 mg/L, and stool occult blood test was positive.

Given the profound cytopenias and clear temporal relationship with azathioprine initiation, acute azathioprine-induced bone marrow suppression was suspected. Azathioprine was discontinued immediately. Supportive therapy was initiated with intravenous hydration, ciprofloxacin and metronidazole for neutropenia-associated infection prophylaxis, and intravenous corticosteroids (prednisolone 40 mg/day) to address presumed concurrent UC activity. Due to symptomatic anemia, he received a unit of packed red blood cells. Owing to thrombocytopenia, clopidogrel was withheld and planned for re-initiation only after platelet counts exceeded 50×10^3/μL.

Despite cessation of azathioprine, the patient's hematologic parameters continued to deteriorate over the next 48 to 72 hours. On the second hospital day, his WBC count fell further to 0.78×10^3/μL and the platelet count decreased to 31×10^3/μL, although his hemoglobin rose to 8.2 g/dL following transfusion. By the third day, marrow suppression reached its peak severity: the WBC count declined to 0.59×10^3/μL, hemoglobin dropped again to 6.4 g/dL in the setting of ongoing gastrointestinal blood loss, and platelets remained critically low at 27×10^3/μL. Throughout this period, the patient remained afebrile and hemodynamically stable, with no focal or systemic signs of infection; although extensive microbiological testing was not available, opportunistic infection was considered clinically, and the subsequent rapid hematologic recovery after azathioprine withdrawal supported drug-induced myelotoxicity rather than an infectious etiology.

Beginning on the fourth hospital day, laboratory values began to show the first signs of marrow recovery. The WBC count increased to 0.87×10^3/μL, platelets rose to 32×10^3/μL, and hemoglobin stabilized with continued supportive management. Clinically, the patient's diarrhea progressively decreased in frequency, and he reported gradual improvement in energy, appetite, and overall well-being. No infectious complications developed during hospitalization.

By the sixth day of admission, hematologic recovery was substantial: the WBC count had increased to 2.21×10^3/μL, hemoglobin to 8.6 g/dL, and platelets to 187×10^3/μL. The rapid rebound in cell counts after withdrawal of azathioprine strongly supported the diagnosis of reversible drug-induced myelosuppression rather than a primary hematologic disorder. Colonoscopy was deferred during this admission due to the elevated bleeding risk associated with thrombocytopenia and mucosal friability.

Once stabilized, the patient was transitioned to oral mesalamine for maintenance therapy, alongside proton-pump inhibitor therapy and calcium supplementation. Plans were made to initiate infliximab as a long-term steroid-sparing strategy after complete hematologic recovery. He was discharged in stable condition with close outpatient gastroenterology follow-up.

At the time of discharge, stool frequency had significantly decreased, bleeding had resolved, and laboratory values were trending toward normalization. At outpatient gastroenterology follow-up four days after discharge, his complete blood count had fully normalized, with restoration of WBC and platelet counts to within reference ranges and complete clinical resolution of diarrhea and bleeding.

Discussion

Azathioprine-induced myelotoxicity is among the most serious complications of thiopurine therapy and remains a major barrier to its long-term use in inflammatory bowel disease.[1,4,7,11] Although controlled trials often cite low rates of severe cytopenia, real-world cohorts consistently report higher toxicity rates, particularly in populations with unrecognized pharmacogenetic susceptibility.[3,5,11]

Azathioprine-induced marrow toxicity results from the accumulation of thioguanine metabolites that disrupt DNA replication in hematopoietic progenitor cells.[10,12,13,15] The degree of toxicity is strongly influenced by pharmacogenetic factors—particularly TPMT and NUDT15 variants—which modulate intracellular levels of active thioguanine nucleotides.[10,12-14,20] Early-onset, profound pancytopenia typically reflects impaired NUDT15-mediated detoxification, leading to rapid accumulation of DNA-incorporated 6-TGNs and apoptosis of marrow precursors.[12-15]

Early-onset myelotoxicity, typically arising within the first two to six weeks of therapy, has become increasingly linked to genetic variants that impair thiopurine metabolism.[4,10,11,21] While TPMT deficiency has historically been emphasized, accumulating evidence identifies NUDT15 polymorphisms—common in Asian and Middle Eastern populations—as a principal contributor to abrupt and profound cytopenias.[13-15] In this respect, the clinical trajectory of our patient, who developed escalating pancytopenia approximately four weeks after initiating standard-dose azathioprine, closely mirrors the characteristic timing and severity described in NUDT15-associated early marrow toxicity. This correlation is noteworthy because pharmacogenetic screening is not routinely implemented in many regions, resulting in patients beginning thiopurine therapy without assessment of genetic vulnerability. In the present case, pharmacogenetic testing for TPMT and NUDT15 variants was not performed, reflecting real-world limitations in test availability at the treating center.

A central teaching point of this case lies in the diagnostic uncertainty generated by the overlap between symptoms of ulcerative colitis exacerbation and manifestations of marrow failure. The patient presented with progressive bloody diarrhea, weakness, and marked fatigue—symptoms that could easily be interpreted as worsening colitis. However, each of these findings may equally reflect severe anemia, thrombocytopenia, or neutropenia.[17-19] This convergence is well recognized in the literature and often leads to misinterpretation.[4,11,18] In our patient, the clinical presentation alone might have prompted escalation of corticosteroids or the addition of further immunosuppression had an early complete blood count not been obtained. Instead, laboratory evaluation revealed severe pancytopenia—WBC 1.08×10^3/μL, hemoglobin 6.7 g/dL, and platelets 45×10^3/μL—which immediately shifted the diagnostic focus toward azathioprine toxicity rather than uncontrolled colitis. This pattern is consistent with reported cases in which early hematologic assessment was decisive in preventing inappropriate treatment intensification and avoiding the potentially catastrophic consequences of untreated marrow aplasia and severe myelosuppression.[4,11,17,18]

The progression of cytopenias in this patient also paralleled the expected kinetics of thiopurine-induced marrow suppression. In published series, hematologic decline often continues for several days despite cessation of azathioprine due to lingering intracellular metabolites.[4,11,18] This phenomenon was clearly observed in our case: the WBC count fell to a nadir of 0.59×10^3/μL and platelets to 27×10^3/μL on the third hospital day, even though the drug had been discontinued immediately upon admission. Recognition of this predictable delayed nadir is crucial, as clinicians must anticipate ongoing marrow suppression to guide monitoring intensity, transfusion thresholds, and infection prophylaxis during the early recovery period. Equally characteristic was the rapid rebound of hematologic parameters following withdrawal of the drug.[4,11,18,19] The literature consistently describes a prompt recovery of marrow function once the offending agent is removed, provided the stem cell compartment remains intact.[4,11,18,19] In our patient, WBC and platelet counts began to increase by the fourth hospital day and had nearly normalized by day six, with complete normalization confirmed at outpatient follow-up four days after discharge. This brisk recovery strongly supports azathioprine-induced myelosuppression as the underlying mechanism, effectively excluding primary hematologic malignancy, aplastic anemia, or other marrow-intrinsic disorders, which typically exhibit a slower or incomplete response.

The clinical course of this case additionally reinforces several principles in the safe use of thiopurines. International guidelines emphasize the need for frequent complete blood count monitoring during the first month of therapy (a period during which early toxicity most often emerges), consideration of lower starting doses in elderly or low–body weight patients, and heightened vigilance when pharmacogenetic testing is unavailable.[4,11,12,18,19] Had such surveillance occurred prior to presentation, the patient's progressive cytopenias might have been detected before reaching severe levels. Furthermore, given the degree of marrow suppression demonstrated here, rechallenge with azathioprine or related thiopurines is contraindicated. Biological therapies, particularly tumor necrosis factor inhibitors, offer safer steroid-sparing alternatives in similar cases and align with contemporary management strategies that prioritize individualized treatment based on risk stratification, comorbidities, and prior drug tolerance.[1-3] The transition planned for our patient reflects this shift toward precision-guided therapy. The absence of pharmacogenetic testing represents a limitation of this report and precludes definitive attribution of toxicity to an underlying enzymatic variant.

In summary, the clinical and laboratory features of this case closely parallel the patterns described in early-onset thiopurine-induced marrow toxicity, particularly in populations in which NUDT15-mediated susceptibility has been reported. The case underscores the diagnostic challenges created by overlapping symptomatology and highlights the indispensable role of early laboratory monitoring in distinguishing flare from toxicity, guiding timely intervention, and preventing life-threatening complications.

Conclusion

Azathioprine-induced marrow myelosuppression is an uncommon but potentially life-threatening adverse effect that may closely resemble an ulcerative colitis flare, particularly during the early phase of therapy. This case underscores how overlapping clinical features—such as fatigue, bloody diarrhea, and general deterioration—can obscure the underlying diagnosis when hematologic evaluation is delayed. The patient's abrupt and profound pancytopenia, its continued progression despite immediate drug withdrawal, and the rapid hematologic recovery thereafter are characteristic of acute thiopurine toxicity, likely reflecting a pharmacogenetic predisposition. Early recognition through timely complete blood count monitoring, especially within the first month of treatment, is essential to prevent progression to severe marrow failure, sepsis, or catastrophic bleeding. Once detected, prompt cessation of azathioprine and appropriate supportive measures typically result in full recovery. Given the severity of toxicity observed, thiopurines should not be reintroduced, and alternative maintenance therapies such as biologic agents should be pursued. This case highlights the importance of integrating clinical vigilance, laboratory monitoring, and individualized treatment strategies when managing patients with ulcerative colitis receiving thiopurine therapy.

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