

CASE REPORT

Suspected azathioprine-induced hypersensitivity pneumonitis in a patient with autoimmune hepatitis: A rare case report

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Clinical Pearls

• Unique Features of the Case:

This case describes a rare delayed pulmonary hypersensitivity reaction occurring after 3 years of azathioprine treatment for autoimmune hepatitis in a young woman.

• Primary Lesson for Clinicians:

Clinicians should consider azathioprine-induced hypersensitivity pneumonitis in patients receiving azathioprine who develop unexplained respiratory symptoms, as early recognition and drug discontinuation can lead to full recovery.

ABSTRACT

Azathioprine (AZA) is a widely prescribed immunosuppressive agent in the long-term management of autoimmune hepatitis (AIH), valued for its steroid-sparing properties and efficacy in maintaining disease remission. While its common adverse effects – such as myelosuppression, hepatotoxicity, and gastrointestinal intolerance – are well-recognized and routinely monitored, hypersensitivity pneumonitis (HP) remains an exceptionally rare but potentially life-threatening complication. Herein, we describe a 21-year-old female patient with AIH diagnosed at age 18. Who developed possible AZA-induced HP during the 3rd year of continuous therapy. We discuss the potential immunopathogenic mechanisms, review the limited literature on AZA-related pulmonary toxicity, and emphasize the importance of early recognition to prevent irreversible lung injury and optimize patient outcomes.

Keywords: Autoimmune hepatitis, azathioprine, drug-induced lung injury, hypersensitivity pneumonitis.

How to cite this article: Ketenci YB, Demiroz H, Akca M, Avcioglu U. Suspected azathioprine-induced hypersensitivity pneumonitis in a patient with autoimmune hepatitis: A rare case report. Hepatology Forum 2026; 7(3):302–305.

Received: August 11, 2025; **Revised:** November 16, 2025; **Accepted:** December 22, 2025; **Available Online:** July 08, 2026

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Introduction

Autoimmune hepatitis (AIH) is a chronic inflammatory liver disease requiring immunosuppressive therapy to control immune-mediated hepatic injury. Azathioprine (AZA), a purine analog immunosuppressant, remains a cornerstone of the maintenance therapy of AIH due to its efficacy and generally manageable side effect profile. Common adverse effects include myelosuppression, hepatotoxicity, gastrointestinal intolerance, and infection risk. However, AZA can rarely cause severe hypersensitivity reactions, including pulmonary toxicity such as hypersensitivity pneumonitis (HP).

HP is an immune-mediated interstitial lung disease characterized by an exaggerated inflammatory response to inhaled or systemic antigens. Drug-induced HP, especially due to AZA, is an underrecognized entity but has been reported mainly in patients treated for inflammatory bowel disease, organ transplantation, and vasculitis. In contrast, AZA-induced HP in patients with AIH is exceedingly rare, with very few documented cases, making the recognition of this adverse event clinically important. Early diagnosis is crucial since withdrawal of AZA generally leads to resolution, whereas delayed recognition can result in serious morbidity or mortality.

We herein provide a detailed overview of the pathophysiology, clinical presentation, diagnostic workup, and management of AZA-induced HP, emphasizing its rarity in AIH and the importance of clinician awareness of this life-threatening but reversible complication.

Case Report

An 18-year-old Caucasian, female taekwondo athlete was being followed up for known hereditary spherocytosis.

When she applied to the emergency room with complaints of jaundice in the eyes and skin, it was seen that aspartate transaminase: 1148 U/L, alanine aminotransferase: 1833 U/L, Gamma Glutamyl Transpeptidase: 106 U/L, alkaline phosphatase: 49 U/L, total bilirubin: 4.56 mg/dL, direct bilirubin: 4.26 mg/dL. Viral hepatitis was excluded, and her history confirmed no herbal or drug use. Vascular systems were normal on portal Doppler ultrasound; the liver size was 187 mm, and the spleen size was 146 mm. Antinuclear antibody

(ANA) was positive with a 1/1000 titer. Antimitochondrial antibody and anti-smooth muscle antibody were negative. Immunoglobulin G: 22.5 g/L. Liver biopsy was done. The biopsy revealed that AIH with mononuclear inflammatory cell infiltration, interface hepatitis, necroinflammatory foci, and pseudo-rosette formation. The diagnosis of AIH was made when the revised original score for AIH was 22 (definite AIH). Methylprednisolone 30 mg orally was initiated. After 2 weeks, the steroid tapering regimen was continued, whereas 50 mg AZA was added. Remission was observed in the 6th month of treatment. In the 3rd year of AZA treatment and the 2nd year of discontinuation of steroid treatment, when she was 21 year old, she presented to the chest diseases clinic with a history of pneumonia-like bronchitis that had been continuing for 3 months. Saturation (room air) and heart rate were normal. There was no pathology in respiratory function tests and echocardiography. Blood count, serum biochemistry values, and C-reactive protein were normal. A high-resolution computed tomography scan of the chest revealed bronchiectasis and atelectasis. Although the radiologic findings were not entirely typical for HP, the exclusion of infectious, cardiac, autoimmune, and environmental causes, together with the marked clinical improvement after AZA withdrawal, supported the diagnosis of AZA-induced pulmonary hypersensitivity (Fig. 1).

To exclude other possible causes of the pulmonary findings, a detailed differential diagnostic workup was performed. Infectious etiologies, including bacterial pneumonia, tuberculosis, viral infections, and fungal diseases, were ruled out based on negative blood cultures, sputum analysis, and serological testing. Cardiac causes such as congestive heart failure were excluded with a normal echocardiographic evaluation and absence of elevated natriuretic peptide levels. Autoimmune and rheumatologic conditions (including systemic lupus erythematosus, sarcoidosis, and vasculitis) were excluded by negative autoimmune serologies (antineutrophil cytoplasmic antibodies, and rheumatoid factor) and absence of compatible clinical features. Environmental and occupational exposures were also carefully questioned and excluded by patient history. Importantly, following the discontinuation of AZA, the patient's respiratory symptoms improved significantly, which strongly supported the diagnosis of AZA-induced HP. Bronchoalveolar lavage and lung biopsy were not performed due to clinical stability and rapid response to AZA withdrawal.



Figure 1. Bronchiectasis and atelectasis on high-resolution thoracic tomography (Bronchiectasis is shown with asterisks. Atelectasis is shown with arrows).

After other causes were excluded, the patient's symptoms began to decrease 10 days after discontinuing AZA, suggesting AZA-related hypersensitivity. One month later, her symptoms had almost completely disappeared. During this period, she started on 500 mg twice daily of mycophenolate mofetil. Transaminase levels remained normal during the 1st year of mycophenolate mofetil treatment. She has no respiratory symptoms now. Informed written consent was obtained from the patient.

Discussion

AZA is metabolized primarily in the liver to 6-mercaptopurine and to active thioguanine nucleotides, suppressing purine synthesis and lymphocyte proliferation. While dose-dependent toxicities such as myelosuppression and hepatotoxicity are well-characterized, hypersensitivity reactions are thought to be immune-mediated and idiosyncratic.^[1] The imidazole moiety of AZA can act as a hapten, triggering delayed hypersensitivity reactions manifesting as fever, rash, arthralgia, and notably, pulmonary involvement, including HP.^[1,2]

Pulmonary toxicity associated with AZA therapy is rare but documented in various systemic illnesses.^[2,3] To our knowledge, there are few case reports and series showing azathioprine-related hypersensitivity pneumonia.^[2,3] The median time to onset ranged from weeks to months after initiation of AZA, consistent with immune sensitization.^[1] Notably, only a minority exhibited leukopenia, distinguishing hypersensitivity reactions from dose-dependent bone marrow toxicity.^[3]

In clinical practice, patients typically develop respiratory symptoms such as cough, dyspnea, fever, and malaise, alongside radiologic findings including bilateral ground-glass opacities and centrilobular nodules on high-resolution computed tomography of the chest, consistent with an HP pattern.^[1,2] This clinical condition can develop within the 1st month of starting the drug or may develop later. Initial use of steroids along with AZA can mask this condition.^[4] Systemic corticosteroids can temporarily suppress the T-cell-mediated alveolar inflammation characteristic of HP, resulting in partial clinical and radiologic improvement and potentially masking early disease manifestations. This effect has been described in prior reviews and guideline discussions of HP management.^[5]

If the patient's history and imaging are inadequate to diagnose the hypersensitivity pneumonitis, bronchoalveolar lavage, lung biopsy, and special antibodies can be studied.^[5] Bronchoalveolar lavage often reveals lymphocytic alveolitis, and lung biopsy may demonstrate non-necrotizing granulomas, confirming the diagnosis.^[1]

The differential diagnosis includes infection, relapse of underlying autoimmune disease, and other drug-induced pulmonary injuries; thus, it is imperative to exclude these causes with appropriate microbiologic testing and disease activity markers.^[1,2] Rechallenge with AZA is contraindicated due to the risk of severe reactions.^[2,3]

Management involves prompt discontinuation of AZA, which in reported cases resulted in rapid symptomatic and radiological improvement within days to weeks.^[2,3] Systemic corticosteroids

may be necessary in severe disease, but are not always required.

^[1] Alternative immunosuppressive agents such as mycophenolate mofetil can be considered for AIH maintenance to avoid recurrence.^[2]

Despite its rarity, recognition of AZA-induced HP is critical, especially in AIH, where respiratory symptoms might be mistakenly attributed to infection or AIH progression. Documentation and publication of such cases contribute valuable knowledge to the literature and aid clinicians in the early identification and optimal management of this serious adverse event.^[2,3]

This report has several limitations. First, bronchoalveolar lavage, lung histology, and drug rechallenge were not performed, so the diagnosis of AZA-induced HP could not be confirmed and remains probable rather than definitive. Second, the radiological pattern was atypical for HP, with bronchiectasis and atelectasis rather than the more classical ground-glass opacities and centrilobular nodules; alternative or structural explanations, including pre-existing or coincidental bronchiectasis, cannot be entirely excluded and may have contributed to the imaging findings. Third, mycophenolate mofetil was introduced during the same period in which respiratory symptoms improved, so its potential confounding contribution to the observed clinical course cannot be fully disentangled from the effect of AZA withdrawal alone.

Conclusion

In conclusion, AZA-induced HP represents a rare but clinically significant complication, particularly in patients with AIH, where respiratory symptoms may easily be overlooked or misattributed to infectious or autoimmune etiologies. This case highlights the need to consider AZA-induced pulmonary toxicity in patients receiving AZA who develop unexplained respiratory symptoms, even after long-term treatment. Early recognition and prompt discontinuation of AZA are paramount to prevent potentially irreversible pulmonary damage and to facilitate rapid recovery, as demonstrated by previous reports.

Although the pathophysiological mechanisms underpinning AZA-induced hypersensitivity reactions remain incompletely elucidated, the immune-mediated nature of the injury highlights the importance of comprehensive diagnostic evaluation and exclusion of alternative causes. Given the paucity of cases documented in the literature, further reporting and study of such adverse events are vital for advancing clinician awareness, informing guidelines for risk stratification, and optimizing therapeutic decision-making in managing AIH. The publication of rare presentations like this case contributes meaningfully to the collective understanding of AZA safety profiles and underscores the continuous need for vigilance in immunosuppressive drug monitoring.

Ethics Committee Approval: This is a single case report, and therefore ethics committee approval was not required in accordance with institutional policies.

Informed Consent: Informed written consent was obtained from the patient.

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

Financial Disclosure: There is no financial support.

Use of AI for Writing Assistance: This article used Grammarly for grammar and semantic corrections, and Perplexity for formatting corrections.

Author Contributions: Concept: UA; Design: UA; Supervision: UA; Funding: YBK; Materials: HD; Data Collection and/or Processing: HD; Analysis and/or Interpretation: YBK; Literature Review: MA; Writing: YBK; Critical Review: MA.

Peer-review: Externally peer-reviewed.

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