

Azathioprine Associated Acute Respiratory Distress Syndrome: Case Report and Literature Review

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Abstract

A 58-year-old Caucasian man treated with azathioprine to prevent rejection of an orthotopic liver transplant, presented to the Carl Hayden VA Medical Center with rapid respiratory decline and appeared septic. He required urgent intubation, mechanical ventilator support and empiric antibiotics. His clinical picture and imaging studies were consistent with acute respiratory distress syndrome; however, extensive infectious work up failed to reveal an offending organism. Review of his current medications implicated azathioprine and upon discontinuation of this agent, the patient made a rapid recovery. He was subsequently extubated, transferred out of the ICU and soon discharged home in good health.

Prescribed for organ transplant rejection and a wide array of autoimmune diseases, azathioprine has been rarely correlated with pneumonitis and rapid respiratory failure. No reported cases were found in which azathioprine was used to treat liver transplant rejection and associated with development of the adult respiratory distress syndrome (ARDS). However, there have been ARDS cases in which azathioprine was used for other purposes. We review all the available cases of azathioprine associated ARDS. The patients in these reports had similar clinical symptoms on presentation as our patient: hypoxia, febrile episodes and rapid development of ARDS with no infectious etiology. Most notable is the rapid resolution of ARDS after discontinuation of azathioprine.

Although azathioprine toxicity related respiratory failure is rare, this correlation should still be considered in the differential for immunosuppressed patients presenting with rapid pulmonary decline. Further studies are needed and warranted to better correlate this connection, but it is imperative to recognize that the relationship exists.

Introduction

Since its first use in 1961, azathioprine (a derivative of 6-mercaptopurine) has been used as a steroid sparing immunosuppressive agent in numerous disorders including prevention of graft rejection for solid organ transplantation (1-2). Azathioprine side effects are commonly gastrointestinal complaints such as nausea and vomiting, occurring in ~19% of patients. Laboratory abnormalities such as leukopenia are also common (17%) with thrombocytopenia and anemia being less common (3-4%) (3).

Hepatotoxicity has been reported as well. Pulmonary toxicity is not usually noted as a side effect (1). Sixteen cases have been reported in the literature implicating azathioprine with pulmonary toxicity (1-2, 4-12). In 10 of these cases, the patient developed acute respiratory distress syndrome (ARDS) (1,2,6,8,9,11).

Pulmonary infections have been the leading cause of complications in immunosuppressed recipients of solid organs (13). Therefore, when a patient presents with respiratory distress, an abnormal chest x-ray and fevers, such infections are high on the differential, but the possibility of lung injury resulting from the immunosuppressive agent is often overlooked (1). We present a case of azathioprine induced ARDS in a liver transplant recipient and review the available ARDS cases associated with azathioprine use.

Case Report

We present a 58-year-old white man with a past medical history of end-stage liver disease due to hepatitis C cirrhosis and hepatocellular carcinoma who received an orthotopic liver transplant (OLT) 9 months prior to presentation. He was being treated with azathioprine 150mg daily and tacrolimus 1.5 mg daily to prevent rejection. He presented to the emergency department 9 months after his transplant with shortness of breath and increasing hypoxia. He was admitted to the intensive care unit where he developed respiratory failure that night requiring intubation and ventilator support. He had fevers as high as 105.1°F. He had pancytopenia with white blood cell count (WBC) 2.3 thousand cells at presentation, hemoglobin (HGB) 9.8 g/dL and platelets (PLT) 119 thousand cells.

Chest x-ray showed bilateral patchy pulmonary infiltrates. CT of the chest was done as well showing bilateral ground glass opacities and diffuse scattered pulmonary consolidations (Figure 1).

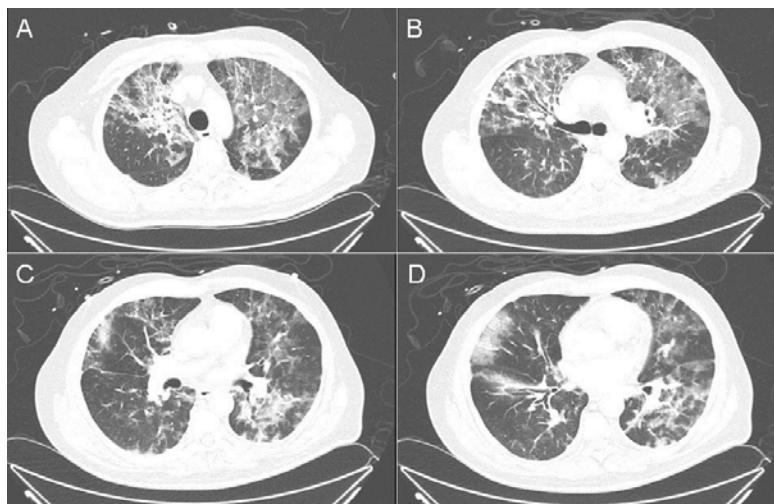


Figure 1. Representative images from chest CT with contrast done on admission showing diffuse ground glass opacities and scattered pulmonary consolidations.

Since he was immunosuppressed he was started on empiric antibiotic coverage with vancomycin, levofloxacin, piperacillin/tazobactam, gancyclovir and fluconazole. Trimethoprim-sulfamethoxazole was added on day 2 of hospitalization. A bronchoscopy with bronchial alveolar lavage (BAL) was done prior to antibiotics. Cell count and differential showed 160 white blood cells, 11% segmented neutrophils and 3% eosinophils, the other 86% of cells were pulmonary macrophages/monocytes and reactive respiratory epithelial cells. No organisms or evidence of malignancy were seen. BAL cultures showed no growth on bacterial, viral, acid fast or mycology cultures. Influenza A and B and a pneumocystis smear were also negative. Blood cultures were taken twice during the patient's hospitalization during febrile episodes and showed no growth both times in two sets of cultures. On day 6 of hospitalization anti-microbial therapy was discontinued.

The patient's clinical status continued to deteriorate. Chest x-rays continued to show increasing bilateral pulmonary infiltrates (Figure 2).

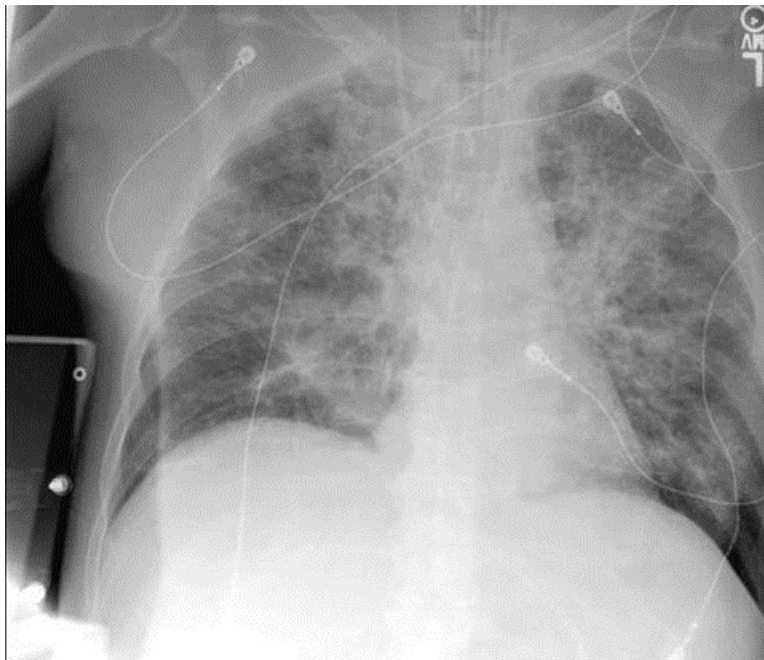


Figure 2. Chest x-ray at worst (hospital day 8) showing worsening bilateral pulmonary infiltrates.

The diagnosis of acute respiratory distress syndrome (ARDS) was established. His ventilator settings followed the NHLBI ARDS Network protocol, and on day 6 he was even placed in a prone position. On day 7 of hospitalization his white blood cell count dropped to a nadir of 0.5 thousand cells, hemoglobin dropped to 6.5 g/dL and platelets down to 69 thousand cells). Azathioprine was discontinued due to the pancytopenia and due to finding a few case reports in which it was implicated in ARDS. Within 3 days of azathioprine discontinuation (day 10 of hospitalization), the patient's chest x-rays and pulmonary function had dramatically improved and he was successfully extubated by

the fifth day of azathioprine being withdrawn (day 12 of hospitalization). Daily chest x-rays showed continued resolution of infiltrates (Figure 3).

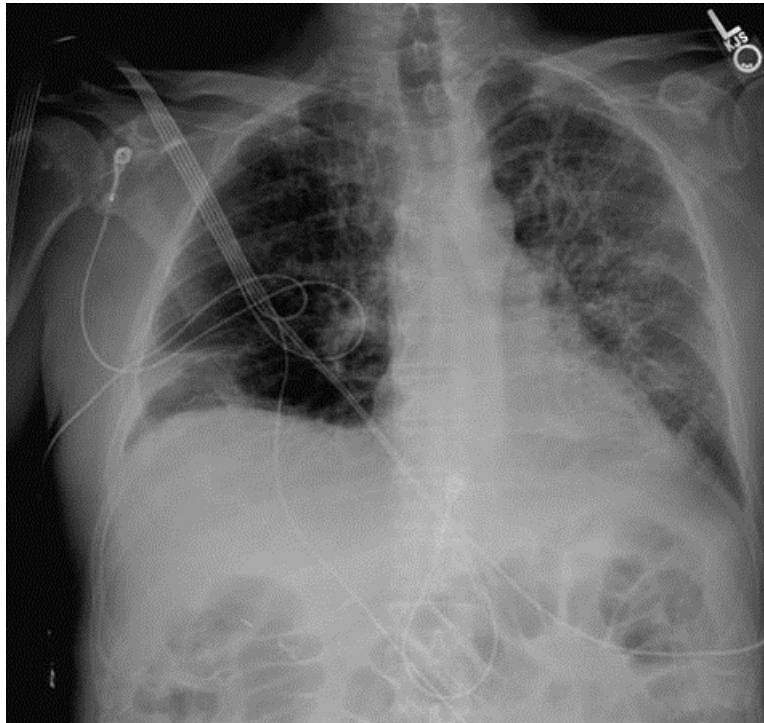


Figure 3. Chest x-ray from hospital day 15 showing dramatic improvement of infiltrates after azathioprine discontinuation.

He improved rapidly and was discharged from the ICU on day 17 and discharged home from the hospital on day 18 with complete resolution of his pulmonary symptoms. His azathioprine was not restarted but he resumed tacrolimus for immunosuppression. Six months after admission, the patient was in good health with no clinical symptoms.

Discussion

Azathioprine is a nitroimidazole derivative of 6-mercaptopurine (4). It was first used in 1961 and has since become a common medication for treatment of numerous autoimmune disorders and as an immunosuppressant in transplant recipients (1). It has been described to have several reversible dose dependent side effects including bone marrow suppression, hepatotoxicity, anorexia, nausea and vomiting (4). Hypersensitivity reactions have also been described and include fevers, rigors, arthralgia, myalgia, cutaneous reactions, headaches, interstitial nephritis, pancreatitis, dyspnea, cough and pneumonitis (1-4, 6).

In our case the patient developed pneumonitis and ARDS which resolved rapidly after the discontinuation of azathioprine. A review of the literature using broad search terms in OVID, Pub-Med and Google Scholar revealed only 10 articles constituting 16 cases of pulmonary toxicity linked to azathioprine. Detailed analysis showed only 5 reported

cases of ARDS linked to azathioprine toxicity (2,6,8,9,11), and a single case series of 7 cases of which 2 also have an infectious etiology (1). Data from these cases are summarized on table 1.

Table 1. Cases of Azathioprine induced ARDS in the literature.

Article	Age (years)	Gender	Indication for AZA therapy	AZA Dose	AZA therapy duration	Improvement after discontinuation?
Bedrossian et al. (1)	51	M	Kidney Transplant	100mg daily	2 months	Died 1 day after
	49	F	Kidney Transplant	50mg daily	3 months	yes
	41	F	Kidney Transplant	25-50mg daily	3 months	yes
	40	F	Kidney Transplant	50mg daily	2 months	yes
	31	F	Kidney Transplant	75mg daily	4 months	Died 2 days after
Weizenburger et al. (2)	24	F	MPGN	150mg daily	2 years	within 1 week
Roubin et al. (6)	20	M	Ulcerative Colitis	100mg daily	4 months	within 2 days
Carmichael et al. (8)	38	F	Kidney/Pancreas Transplant	50-75mg daily	4 months	within 6 days
Perreaux et al. (9)	13	F	Autoimmune Hepatitis	1.4mg/kg	6 weeks	within 2-3 weeks
Brown et al. (11)	58	M	Kidney Transplant	150mg daily	3 months	within 8 days

The four remaining articles not appearing in table 1 were excluded because they either represented an immediate hypersensitivity reaction to azathioprine or had infectious pneumonitis which could have contributed to the development of ARDS (4,5,10,12). Neither our case nor those in the literature contain irrefutable proof that azathioprine was directly responsible for lung injury. However, the similarities between the cases in which the patient survived lead us to conclude that azathioprine is involved in this adverse reaction. First, all 8 cases in which the patient survived show a rapid improvement within one to two weeks after discontinuation of azathioprine. Second, all of these patients present in the same way with hypoxia, pulmonary infiltrates, and fevers. Third, none of the cases show any other possible causes and the ones that go to biopsy have non-specific findings (UIP or diffuse alveolar damage) (1,2,6,7,11). These observations are circumstantial, but the diagnosis of drug-induced pulmonary toxicity is usually based on clinical history of drug exposure and the absence of other known causative agents. Additionally, diffuse interstitial pulmonary disease is the most common form of lung pathology caused by drugs (1,14).

Leukopenia or pancytopenia were present in our case as well as 4 of the 10 reported cases (6,8,9,11). No other side effects from azathioprine were reported in any of the cases. Therefore ARDS is likely a unique effect and unrelated to other potential side effects of azathioprine. The dose of azathioprine was widely variable in the known cases (25-150mg daily) leading us to believe that the development of ARDS is not dose-dependent. All of the cases had patients who had been on azathioprine for months (years in one case) prior to developing pneumonitis or ARDS, leading us to speculate that ARDS is not an acute hypersensitivity. It may be that ARDS development is a function of dose effect over time.

Although there are very few reported cases, It is possible that azathioprine induced lung injury is more common than it appears. When an immunosuppressed patient presents

with respiratory distress, some form of infectious etiology is usually involved and the immunosuppressants are often discontinued (1). It is possible that in some of these cases azathioprine itself is the cause or may at least contribute to the development of ARDS. We believe it is important that azathioprine lung toxicity be included in the differential for ARDS causes because prompt discontinuation of azathioprine has led to rapid recovery and good outcome in 8 of the 10 known cases (1,2,6,8,9,11).

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