Severe Pulmonary Toxicity After Azathioprine/6-Mercaptopurine Initiation for the Treatment of Inflammatory Bowel Disease

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Abstract: Azathioprine and 6-mercaptopurine (6-MP) are effective in inflammatory bowel disease (IBD). However, between 10% and 29% of patients treated with these drugs are forced to stop therapy due to side effects. Pulmonary toxicity due to azathioprine/6-MP has been reported infrequently. We describe 3 patients who developed severe, noninfectious pulmonary toxicity within 1 month after the initiation of azathioprine or 6-MP for the treatment of IBD colitis (2 Crohn's disease and 1 ulcerative colitis). All patients presented with dyspnea, cough, and fever after initiation of azathioprine/6-MP. Evaluation for infectious etiologies, including bronchoscopy (3/3 patients) and open-lung biopsy (2/3 patients) was negative. Histopathologic examination of the lung biopsies revealed bronchiolitis obliterans organizing pneumonia in one, and usual interstitial pneumonitis in another patient. Cessation of purine analog therapy resulted in clinical improvement in all 3 cases. Azathioprine/6-MP–related pulmonary toxicity is a rare but serious side effect, and it is important for clinicians to have a high index of suspicion for this adverse reaction which occurs within 1 month after initiation of treatment for IBD.

Key Words: azathioprine, 6-mercaptopurine, purine analog, pulmonary toxicity, inflammatory bowel disease, Crohn's disease, ulcerative colitis, bronchiolitis obliterans, organizing pneumonia, BOOP, adverse drug reaction

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The purine analogs azathioprine and 6-mercaptopurine (6-MP) are effective for inducing and maintaining remission in inflammatory bowel disease (IBD; Crohn's disease, ulcerative colitis).1–4 However, these agents are frequently associated with a number of adverse effects which may be severe.5 Between 10% to 29% of patients treated with azathioprine or 6-MP are forced to stop the drug because of adverse reactions.2,5–7 These adverse reactions can be categorized into 2 types—allergic, dose-independent, and nonallergic, dose-dependent toxicities.4 In a large meta-analysis, azathioprine use was associated with allergic type reactions in 2% of patients.2 These reactions usually present with fever, arthralgias, and myalgias,8,9 but may also manifest with serious complications including pancreatitis and hypotension.9

Dose-dependent azathioprine toxicity most frequently manifests as myelosuppression leading to leucopenia and thrombocytopenia, hepatitis, and infections.8,9 Pulmonary toxicity due to azathioprine has been infrequently reported in the literature, especially in patients with IBD.10,11 Severe pulmonary adverse reactions to azathioprine and 6-MP include interstitial pneumonitis,11–13 restrictive lung disease,10 Goodpasturelike syndrome, and pulmonary hemorrhage.14 Pulmonary involvement is a rare but recognized extraintestinal manifestation of IBD.15 and may include airway disease, tracheal obstruction, chronic bronchitis, bronchiolitis obliterans,16 interstitial lung disease, pulmonary nodules, Wegener granulomatosislike symptoms,17 or serositis.15 Isolated cases of drug-induced pulmonary toxicity have been described in IBD patients and have focused primarily on sulfasalazine and mesalazine, which have been linked with small airway disease including bronchiolitis obliterans.15,17–19

We reviewed our IBD Center's database to identify individuals who experienced severe pulmonary toxicity within 1 month after the initiation of azathioprine or 6-MP therapy. We identified 3 patients who developed severe, noninfectious pulmonary complications and describe their clinical course, and also review that current literature on pulmonary toxicity owing to purine analog therapy. This retrospective review was approved by the Medical College of Wisconsin’s human research review committee.

CASE SERIES

Case 1

The patient was a 66-year-old man with a 4-year history of Crohn's colitis. He initially experienced bright red bleeding...
per rectum and required treatment with oral corticosteroids, which were unable to be weaned below 10 mg of prednisone daily. The patient had been treated with oral mesalamine 2.4 grams daily for 2 years with limited benefit, and no pulmonary side effects were noted during this prolonged treatment period. Mesalamine treatment was stopped because of the lack of efficacy and an attempt to use azathioprine (starting dose 50 mg daily) as a steroid-sparing agent was made. This was unsuccessful, as the patient developed a "fulminic" illness characterized by fevers and myalgias within 4 weeks after the initiation of low-dose azathioprine. After the cessation of azathioprine, the patient was treated with infliximab. He demonstrated a transient response to episodic infliximab infusions, which were discontinued after the third treatment. Over the ensuing 2 months, his bowel symptoms returned but then improved with increased corticosteroid use, requiring prednisone dosages above 20 mg daily to maintain clinical response. This resulted in diabetes mellitus requiring insulin injections and significant weight gain. For these reasons, 6-MP 100 mg daily was tried as a potential steroid-sparing agent. The patient received this "rechallenge" with the alternate purine analog in an attempt to establish a maintenance immunomodulator. Four weeks after the initiation of 6-MP, the patient presented to the emergency room with complaints of cough, shortness of breath, and fever, which had worsened over a 2-week period. At the time of presentation, his white blood cell (WBC) count was 8400/mm³, but within 24 h it had increased to 17,000/mm³ with 91% neutrophils. Additional laboratory parameters including serum chemistries and liver tests were normal. Other medications at the time of admission included lansoprazole, prednisone 30 mg daily, tamsulosin (Flomax; Boehringer Ingelheim Pharmaceuticals Inc, Ridgefield, CT) and alprazolam. Although 6-MP was discontinued at the time of admission, the patient's clinical condition rapidly deteriorated and he required intubation within 24 hours for respiratory failure and hypoxia. Chest x-ray revealed diffuse patchy interstitial infiltrates that were confirmed with a chest computed tomography (CT). Bronchoscopy with lavage and biopsy was performed which failed to detect an infectious etiology. Specific tests for cytomegalovirus, herpes viruses, pneumocystis carinii and also bacterial and fungal infections were also negative. An open-lung biopsy was performed and tissue samples were obtained from the right lower lobe. Histologic examination revealed nonspecific interstitial pneumonitis with diffuse alveolar damage. Again no infectious etiology could be identified. The dose of intravenous corticosteroids was increased and the patient continued to be treated with empiric trimethoprim-sulfamethoxazole, acyclovir, and azithromycin. He was extubated after 1 week of ventilatory support. He continued to be mildly hypoxic after extubation and was discharged with supplemental oxygen. Three months after discharge, the patient still manifested a persistent mild restrictive defect with moderate decrease in diffusion lung capacity (DLCO). Repeat pulmonary function tests performed 10 months after discharge revealed a DLCO of 12.6 mL/min/mm Hg (49% of predicted), forced expiratory volume (FEVi) 2.37 L (77% of predicted), and forced vital capacity 3.13 L (70% of predicted). The patient continued on corticosteroids for the treatment of his Crohn's disease and ultimately underwent total abdominal colectomy and permanent end-ileostomy, which allowed for discontinuation of these agents.

Case 2

A 71-year-old white man with a 12-year history of Crohn's colitis presented with an acute flare. His past medical history was otherwise benign. The patient had been treated with prednisone 10 mg daily by a family physician for an 8 year time period. At the time of the disease flare, he was treated with an increased dosage of prednisone and mesalamine over a 3-month period, with no improvement. Mesalamine was then discontinued. Because of inability to taper prednisone to less than 20 mg/d, azathioprine 100 mg/d was initiated as a steroid-sparing strategy. Within 2 weeks after the start of azathioprine, the patient developed fever, worsening diarrhea, and abdominal pain. He was hospitalized for an acute flare of Crohn's disease and was initially managed with intravenous corticosteroids. Because of lack of response, the patient was also given an infliximab infusion and later intravenous cyclosporine A, neither of which produced clinical improvement. Throughout this hospitalization the patient continued to receive azathioprine. During the hospital stay, he developed a progressively worsening nonproductive cough, fever, shortness of breath, and required supplemental nasal cannula oxygen to maintain saturation. His peripheral smear revealed leukocytosis (> 20,000/mm³). A CT of the chest demonstrated ground glass opacities affecting predominantly the upper lobes bilaterally (Fig. 1). A bronchoscopy was performed to identify possible infections, but was negative for bacterial, viral, fungal pathogens, and pneumocystis carinii. This prompted an open-lung biopsy, which demonstrated an acute inflammatory process associated with numerous neutrophils, vasculitis, and patchy areas of necrosis and also fibrinous exudates. Histologic features were suggestive of bronchiolitis obliterans with organizing pneumonia (BOOP) (Fig. 2). The lung tissue samples again did not reveal an infectious etiology. After the open biopsy the patient was continued on broad-spectrum antibiotics, intravenous corticosteroids, and azathioprine. During this period of severe illness, he experienced 60 lbs in weight loss.

The patient was ultimately transferred to our institution, at which time he was found to have elevated WBC counts of 27,000/mm³, low serum albumin (< 2 g/dL) as well as fever to 40°C. Immediately after transfer azathioprine was discontinued, and within 3 days of cessation, the WBC count normalized to 8000/mm³, which was accompanied by resolution of fevers. The patient required an additional 2-month hospitalization, with parenteral nutrition and ultimately colectomy and end-ileostomy, with improvement in his clinical status. Corticosteroids were gradually tapered over 6 months and the patient had complete recovery of his pulmonary function.

Case 3

A 43-year-old woman with a history of left-sided ulcerative colitis presented with complaints of generalized malaise, in addition to a week-long history of dry, nonproductive cough, and shortness of breath. Three weeks prior, the patient had initiated treatment with azathioprine at 100 mg daily. She had been diagnosed with ulcerative colitis 7 years prior, which had initially responded to oral corticosteroid taper. The patient had experienced a prolonged remission with mesalamine, with only one additional disease flare requiring corticosteroid therapy. During the months before the present admission, she had experienced a progressive deterioration with active colitis, and had reinitiated oral prednisone, which was unable to be tapered over a 2-month period. In hopes of a steroid-sparing effect, azathioprine had been initiated at 100 mg daily, and this had been started while the dosage of prednisone had been increased to 40 mg daily.

Because of increasing symptoms of cough and shortness of breath, the patient sought evaluation in a walk-in emergency
room, where she received a prescription for oral antibiotics. Over the next 24 hours she continued to deteriorate, ultimately requiring a second emergency room evaluation during which she was found to be cyanotic and hypoxic, requiring immediate intubation and mechanical ventilation. Chest x-ray and CT scan were consistent with right middle lobe pneumonia with additional bibasilar consolidation. Microbiologic studies, which included tests for *pneumocystis carinii*, bacterial, viral and fungal cultures, and bronchoscopic studies were all negative. Azathioprine was discontinued at the time of admission and the patient was started on high-dose intravenous hydrocortisone along with levofloxacin. She improved and was weaned off the ventilator 5 days later. She was discharged on oral prednisone and levofloxacin. Her respiratory function returned to normal.

**FIGURE 1.** Purine analog pulmonary toxicity in a 71-year-old man on azathioprine for the treatment of Crohn’s disease. Axial CT of chest demonstrates ground glass opacities affecting predominantly the upper lobes bilaterally (arrow). This type of infiltrate is nonspecific but can be seen in drug-related toxicities or reactions.

**FIGURE 2.** Histologic appearance of an open-lung biopsy specimen showing purine analog induced pulmonary toxicity in a 71-year-old man whose CT findings are shown in Figure 1. A, Low power magnification, hematoxylin and eosin (H&E) stain: large area of acute bronchopneumonia showing early organization by granulation tissue. Many alveolar walls are covered by fibrin exudates. B, High power magnification, H&E stain: organizing pneumonia. Lower portion of the figure shows neutrophils in alveolar space. C, High power magnification, H&E stain: arteritis of pulmonary artery. Acute, especially eosinophils, and chronic inflammatory cells are within the wall of a pulmonary artery.
quickly after discharge. Ulcerative colitis remained poorly controlled on corticosteroids and ultimately required abdominal colectomy and end-ileostomy, followed by ileo-anal J pouch reconstruction. Purine analog therapy was never reattempted.

**Review of Literature**

We performed a literature search on the MEDLINE database to evaluate all articles describing pulmonary toxicity associated with azathioprine or 6-MP treatment published in the time period 1966 to April 2006. A total of 10 case reports or case series describing 16 patients that reported pulmonary adverse effects after azathioprine use were identified (Table 1).10-14,20-24 There were no reports of pulmonary toxicity associated with 6-MP. A majority of the case reports were in adult patients, whereas 2 of the case reports were in children.14,22

**DISCUSSION**

We report a series of IBD patients who developed severe, noninfectious pulmonary toxicity during the first month after the initiation of azathioprine or 6-MP for the treatment of moderate to severe IBD colitis. Our report highlights an important and potentially devastating adverse reaction that may arise in Crohn’s disease or ulcerative colitis patients who are started on this well-established regimen for control of IBD. There are limited reports regarding pulmonary toxicity after the initiation of azathioprine and 6-MP; our report is the first case series describing severe pulmonary failure requiring ventilator support. Careful evaluation for potential infectious etiologies including bronchoscopy (3/3 patients) and open-lung biopsy (2/3 patients) did not demonstrate an infectious etiology for respiratory failure and severe systemic illness in any of these individuals. Clinical improvement was associated with cessation of purine analog therapy in all 3 of these individuals, emphasizing the importance of a high index of suspicion for this rare adverse drug reaction.

The first reported case of azathioprine related pulmonary toxicity was by Rubin et al10 in 1972 when they described a 20-year-old man with Crohn’s disease who presented with exertional dyspnea. Spirometry performed during the acute episode revealed decreased FEV and forced vital capacity. Bronchoscopy failed to reveal a definitive etiology for the deteriorating lung function. However, 2 days after cessation of azathioprine his fevers resolved and pulmonary function improved. He was treated with an increased dose of prednisone, which led to complete resolution of symptoms. Another case of azathioprine related toxicity in an IBD patient was described by Krowka et al14 in 1983 in a 35-year-old man who presented with intermittent fever. Gallium scan revealed diffuse uptake in the lungs bilaterally and bronchoscopy with transbronchial biopsy showed alveolitis. The patient was treated with oral prednisone and improved within 6 weeks after stopping the azathioprine. Neither of the patients experienced pulmonary failure requiring ventilator support, which was seen in our series.

The largest description of pulmonary toxicity related to azathioprine use was a case series by Bedrossian et al12 who described 7 patients on azathioprine for cadaveric renal allograft transplant immunosuppression. These patients developed fever, shortness of breath, and hypoxia. Lung biopsies revealed usual interstitial pneumonitis in 5 and diffuse alveolar damage in the remaining 2 patients. Three of the patients died within 2 days of biopsy and 1 patient died 30 days after. The other patients improved after discontinuation of azathioprine and cyclophosphamide was necessary for the treatment of pneumonitis in an additional 2 patients.

Most cases of pulmonary toxicity attributed to azathioprine use have been seen in patients undergoing renal allograft transplantation. However Weisenburger24 reported a case of acute interstitial pneumonitis in a patient on azathioprine for membranoproliferative glomerulonephritis. Stetter et al32 described an acute hypersensitivity-like reaction mimicking Goodpasture syndrome in a 27-year-old man after renal transplant.

Infectious pneumonia is most common cause of pulmonary symptoms in IBD patients on immunosuppressive therapy including azathioprine. Although some recent and older randomized controlled trials of azathioprine in over 100 IBD patients did not report any episodes of severe pneumonia,6,25-28 other authors have reported a 1% to 10% incidence of pneumonia in patients on azathioprine.29,30 Other drugs used in the treatment of IBD patients have also been reported to cause pulmonary disease. Infliximab has been increasingly associated with infectious pulmonary complications including tuberculosis and *pneumocystis carinii* pneumonia.31 However, there are only a few case reports of noninfectious pulmonary complications due to infliximab use numbering less than 15 patients so far in the literature, especially in IBD patients. Acute respiratory distress syndrome,32 diffuse alveolar hemorrhage,33 and BOOP, interstitial pneumonitis34 have been reported in literature. In a paper by Ostor et al34 recently which is the largest case series of pulmonary toxicity from infliximab, 3 of the 5 patients were on concomitant azathioprine and 2 were on leflunomide which has also been associated with pulmonary toxicity. We also found only 1 case report of interstitial pneumonitis due to cyclosporine in the literature.35

Purine analog-related pulmonary toxicity seems to be a rare but serious side effect of these drugs. It may present as pneumonitis or diffuse alveolar damage, but other presentations including pulmonary hemorrhage have also been described in the literature. Our report of 3 cases adds to the growing description of pulmonary adverse effects after the initiation of azathioprine and is the initial report of severe pulmonary toxicity following 6-MP treatment. Although there is no confirmatory finding for ascribing the pulmonary pathology directly to azathioprine or 6-MP use, the lack of an infectious or alternative etiology, the temporal relation with purine analog initiation, resolution with drug cessation and clinical and pathologic correlation with previously
<table>
<thead>
<tr>
<th>Report Number (Reference No.)</th>
<th>No. Patients</th>
<th>Age/Sex</th>
<th>Underlying Disease</th>
<th>Clinical Symptoms</th>
<th>Lung Bx</th>
<th>Pulmonary Disease</th>
<th>Treatment</th>
<th>Interval Between Drug Initiation and Pulmonary Symptoms</th>
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<td>20/M</td>
<td>Ulcerative colitis</td>
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<td>Acute restrictive pulmonary disease</td>
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<td>Fever, dry cough, dyspnea</td>
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<td>Acute interstitial pneumonitis</td>
<td>Corticosteroids, cephalothin</td>
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<td>Crohn’s disease</td>
<td>Intermittent fever</td>
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<td>Alveolitis</td>
<td>Prednisone</td>
<td>4 mo</td>
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<td>4 (20)</td>
<td>1</td>
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<td>Renal transplant</td>
<td>Rigors, fever, sneats</td>
<td>Y</td>
<td>Acute interstitial pneumonitis</td>
<td>Prednisolone, cyclosporine</td>
<td>4 mo</td>
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<td>5 (12)</td>
<td>7</td>
<td>74/M</td>
<td>Renal transplant</td>
<td>Fever, hypoxia</td>
<td>Y</td>
<td>Usual interstitial pneumonitis (5); diffuse alveolar damage (2)</td>
<td>3 patients died within 2 d of lung biopsy, another died 30 d later. Consolidation cleared in 1 patient after the discontinuation of azathioprine, others were treated with cyclophosphamide</td>
<td>35 to 229 d</td>
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<td>Acute interstitial pneumonitis</td>
<td>Cyclophosphamide, discontinuation of azathioprine</td>
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<td>Fever, hemoptysis, hypoxia</td>
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<td>Pneumonitis</td>
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<td>Fever, rigors, hemoptysis</td>
<td>Y</td>
<td>Good pasture syndrome-like hypersensitivity</td>
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<td>Fever, rigors, hemoptysis</td>
<td>Y</td>
<td>Good pasture syndrome-like hypersensitivity</td>
<td>Discontinuation of azathioprine</td>
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<td>40/M</td>
<td>Ulcerative colitis</td>
<td>Fever, cough</td>
<td>Y</td>
<td>Interstitial pneumonitis</td>
<td>Discontinuation of azathioprine, steroids</td>
<td>—</td>
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<td>Crohn’s disease, ulcerative colitis</td>
<td>Fever, dyspnea, cough</td>
<td>Y (2/3)</td>
<td>BOOP* (1/3), usual interstitial pneumonitis (1/3)</td>
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<td>2 to 4 wk</td>
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*Membranoproliferative glomerulonephritis.  
†Bronchiolitis obliterans with organizing pneumonia.  
‡Present case series.
reported cases in literature, indicate that a drug-related adverse effect was the likely etiology. One of our patients was rechallenged with a purine analog, which resulted in a rapid deterioration and severe systemic and pulmonary illness. This individual had demonstrated sensitivity to low-dose azathioprine with fevers and myalgias, and the subsequent attempt at weight-based dosing with 6-MP correlated with a more severe adverse reaction. All 3 patients in our series had no pulmonary symptoms attributable to IBD before the initiation of azathioprine/6-MP therapy. Two of our patients recovered completely, but 1 individual had moderate residual pulmonary sequelae. Similar to prior descriptions in the literature, our cases responded to discontinuation of azathioprine/6-MP and high doses of oral or intravenous corticosteroids. The importance of discontinuing the offending agent makes it essential for physicians to recognize this adverse reaction early in its clinical course, which may occur in patients who are initiating purine analog therapy.

The ameliorating effect of corticosteroids in inflammatory lung injury may inadvertently mask severe purine analog pulmonary adverse reactions. All 3 of our patients were receiving dosages of prednisone greater than 20 mg daily when the severe pulmonary adverse reaction initially manifested. Therefore, clinicians must have a high index of suspicion for potential severe drug adverse reaction in addition to opportunistic pneumonia, in the setting of pulmonary complications occurring in IBD patients. A history of recent purine analog (ie, azathioprine or 6-MP) initiation in the setting of diffuse pulmonary infiltrates, fever, hypoxia, and respiratory failure warrants immediate cessation of the possible offending drug to prevent progression of symptoms and catastrophic outcome.

In summary, severe adverse pulmonary injury is a rare complication of the purine analogs azathioprine and 6-MP, which may occur within the first month after the initiation of treatment in patients with IBD. Pulmonary failure within 1 month of purine analog initiation should prompt clinicians treating IBD to suspect this devastating adverse reaction. Ventilator support, high-dose corticosteroid treatment and cessation of the offending agent in addition to the careful assessment for potential infectious complications are important considerations for optimal clinical outcome.

REFERENCES


