

# Pulmonary Eosinophilia Following Infliximab Treatment for Crohn's Disease

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An 18-year-old woman with a history of asthma and Crohn's disease of the terminal ileum and colon with prior perirectal abscess, who was on azathioprine and infliximab (Remicade, Centocor) therapy, presented with sore throat, fevers, dyspnea, and nonproductive cough 2 weeks after her third infusion of infliximab. Laboratory studies demonstrated a peripheral eosinophilia of 29% and chest radiograph and computed tomography scan revealed bilateral diffuse infiltrates. Bronchoscopy with bronchoalveolar lavage and transbronchial biopsy showed interstitial and intra-alveolar eosinophilic infiltrates consistent with an eosinophilic pneumonia. Infectious etiologies were ruled out. The patient was treated with a short corticosteroid taper and symptoms, eosinophilia, and infiltrates resolved. Infliximab therapy was discontinued but she was maintained on azathioprine therapy. At 19 months follow-up, she remains without pulmonary symptoms, and eosinophil count is 1%. Infliximab has been associated with an eosinophilic reaction in two previous reports. Clinicians should be aware of the possible association between infliximab infusion and pulmonary eosinophilia.

## Case Report

An 18-year-old nonsmoking woman presented with a 1-week history of fever, nonbloody diarrhea, and perianal pain. She had a history of mild intermittent asthma, controlled with montelukast. Laboratory tests revealed a leukocytosis (17 K/uL) and anemia (hemoglobin 7.8 g/dL); stool cultures were negative. Ciprofloxacin was prescribed without benefit. Subsequent colonoscopy identified inflammation of the distal ileum, ileocecal valve, and

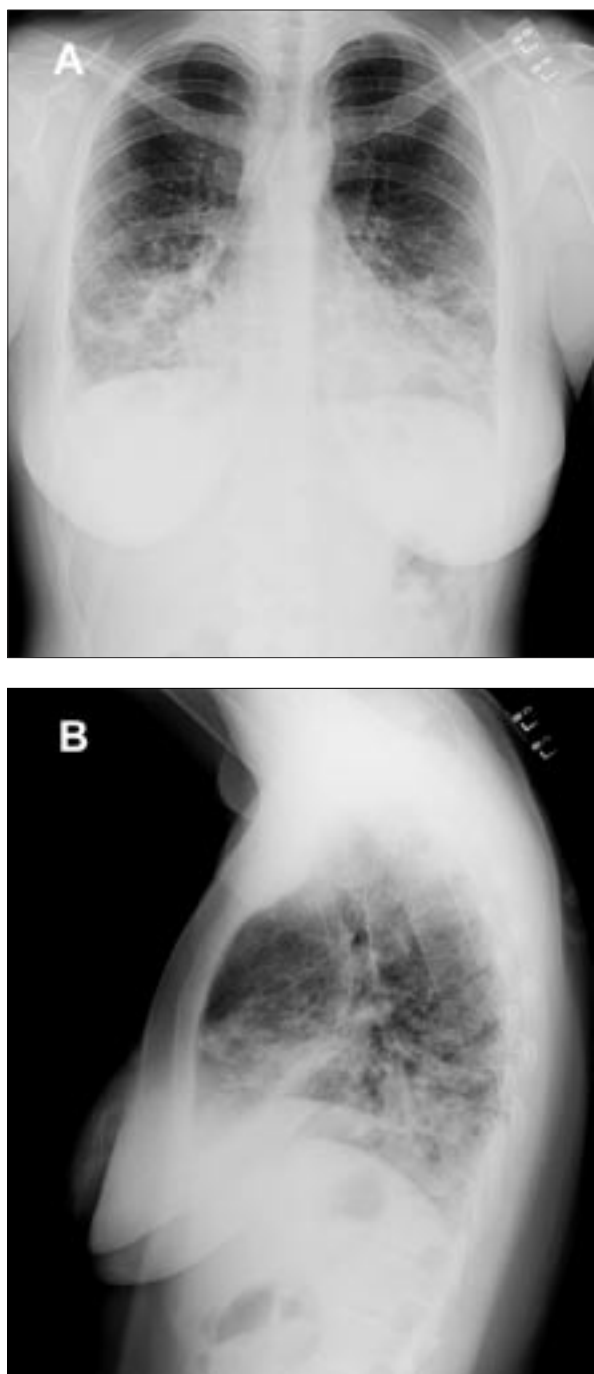
ascending colon, as well as distal rectal erosions; biopsies were consistent with a diagnosis of Crohn's disease. Computed tomography (CT) scan of the abdomen and pelvis revealed a perirectal abscess, which was drained under CT guidance. Additional evaluation included a barium small bowel series, which demonstrated a 12 cm ileal stricture. The patient was treated with intravenous hydrocortisone as well as ciprofloxacin and metronidazole. She was discharged on a prednisone taper and these antibiotics but fevers and perirectal pain returned; a repeat CT scan of the abdomen and pelvis showed persistent perirectal and terminal ileal inflammation but no recurrent abscess. She was readmitted to the hospital for intravenous hydrocortisone and observation. Due to the severity of her disease as well as the perianal penetrating disease, both azathioprine (2.5 mg/kg/day administered orally [PO]) and infliximab (5mg/kg administered intravenously [IV]) therapy were initiated in the inpatient setting. A pretreatment purified protein derivative (PPD) test was negative.

Additional induction infusions of infliximab at weeks 2 and 6 were administered without complication. However, 2 weeks after her third infliximab infusion, she presented to an outside clinic with a 2-day history of sore throat, fevers, and dyspnea with nonproductive cough. Empiric treatment with ciprofloxacin resulted in nausea and vomiting, and she was admitted to the hospital. Admission laboratories revealed a white blood cell count of 18.4 K/uL, and a chest radiograph demonstrated bibasilar infiltrates. Therapy was then changed to ceftriaxone and azithromycin for presumed community-acquired pneumonia, and azathioprine was held. The patient continued to have fevers (101.4° F), and leukocytosis persisted (19.5 K/uL). Three days after presentation, she was transferred to our institution for further evaluation.

On transfer, the patient had ongoing fevers, cough, and dyspnea, as well as new nonbloody diarrhea; CT scan of the abdomen and pelvis showed inflammation of the

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**Figure 1.** Chest radiograph showing bibasilar infiltrates: PA view (A) and lateral view (B).

terminal ileum with no evidence of fistula, abscess, or sinus tract formation. Laboratory studies showed a white blood cell count of 9.4 K/uL with a newly developed, marked eosinophilia (differential included 52% neutrophils, 1% bands, 8% lymphocytes, 8% monocytes, and 29% eosinophils). Stool examination for ova and parasites was negative. A chest radiograph confirmed bibasilar infil-

trates (Figure 1); ceftriaxone and azithromycin were continued. Chest CT scan revealed a diffuse patchy nodular infiltrate in all lung fields with dense consolidation in the lower lobes concerning for pulmonary hypersensitivity or Wegener granulomatosis (Figure 2). Antineutrophil cytoplasmic antibody (ANCA) studies were negative.

Two days after admission, bronchoscopy with bronchoalveolar lavage (BAL) and transbronchial biopsy (TBB) was performed. The airways appeared normal, with minimal secretions. Gram's stain, bacterial, fungal, and viral cultures, and special stains for Cytomegalovirus, *Pneumocystis* and acid fast bacilli (AFB) were negative. TBB demonstrated interstitial and intra-alveolar eosinophilic infiltrates with giant cells and Charcot-Leyden crystals (Figure 3). There was no evidence of vasculitis or granuloma formation. This was thought to be most consistent with eosinophilic pneumonia.

Prednisone 60 mg PO daily was begun for the eosinophilic pneumonia. The patient's symptoms, including the diarrhea, improved during the course of her hospitalization. She was discharged 4 days after admission on a 7-day prednisone taper, with complete resolution of pulmonary symptoms and the eosinophilia (1% on the day of discharge). Infliximab therapy was discontinued but azathioprine was resumed.

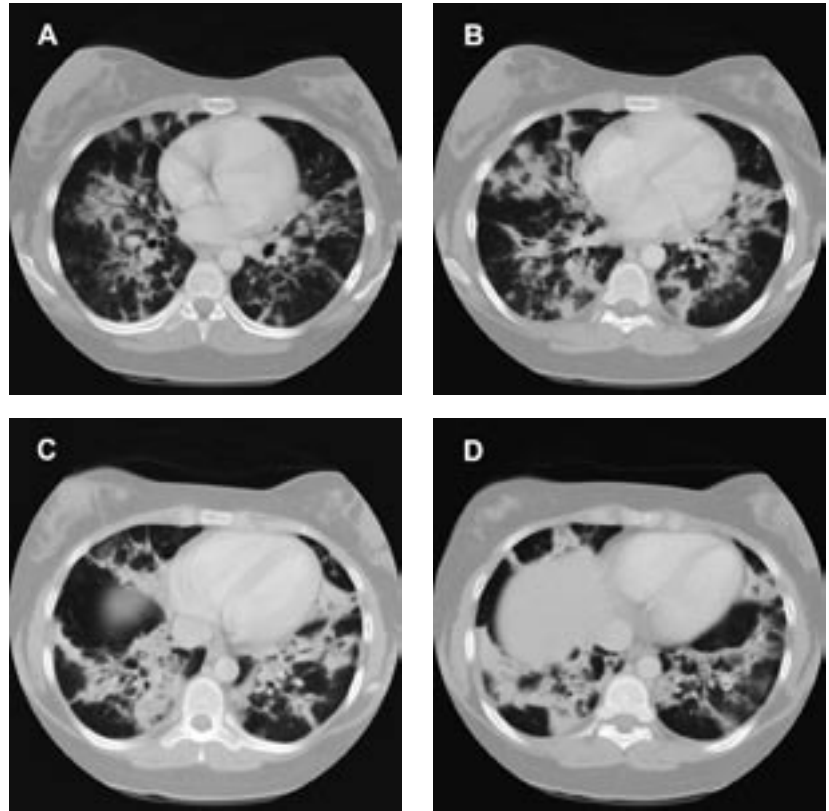
On 3-month follow-up, chest radiographs showed resolution of the pulmonary infiltrates (Figure 4) and peripheral eosinophil count remained low (8%). Immunoglobulin E (IgE) level was slightly elevated at 196 IU/mL (normal <100 IU/mL). Pulmonary function testing 2 months after discharge showed a mild obstructive pattern consistent with her underlying asthma (Table 1), which remained well-controlled on montelukast. Remission of Crohn's disease was maintained on azathioprine 200 mg PO daily. Nineteen months later, the patient's eosinophil count is still low (1%), and she continues to be free of pulmonary symptoms but has required ileocecectomy for obstructive ileal disease and recovered without complication.

## Discussion

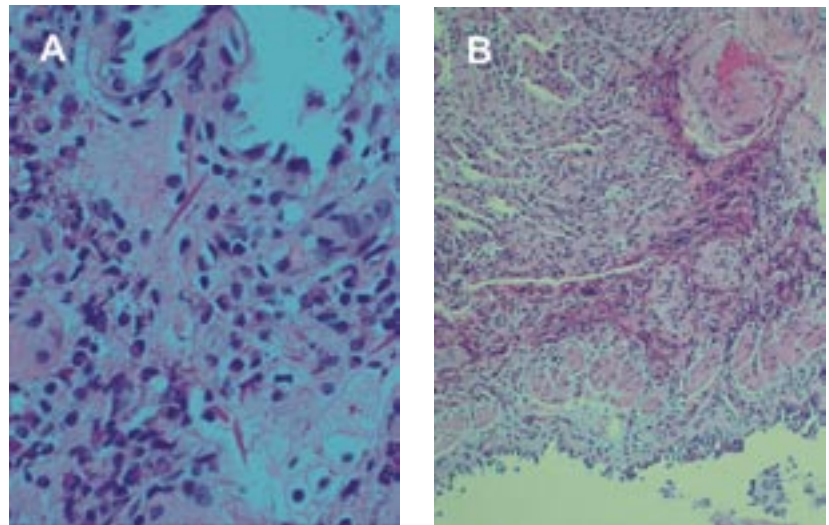
A variety of adverse pulmonary effects have been reported following infliximab infusion, including latent tuberculosis reactivation,<sup>1</sup> invasive aspergillosis,<sup>2</sup> interstitial pneumonitis, pulmonary edema, and alveolar hemorrhage.<sup>3</sup> This patient developed eosinophilic infiltrates with pneumonia shortly after her third infliximab infusion, which resolved with a short course of corticosteroids and discontinuation of infliximab therapy.

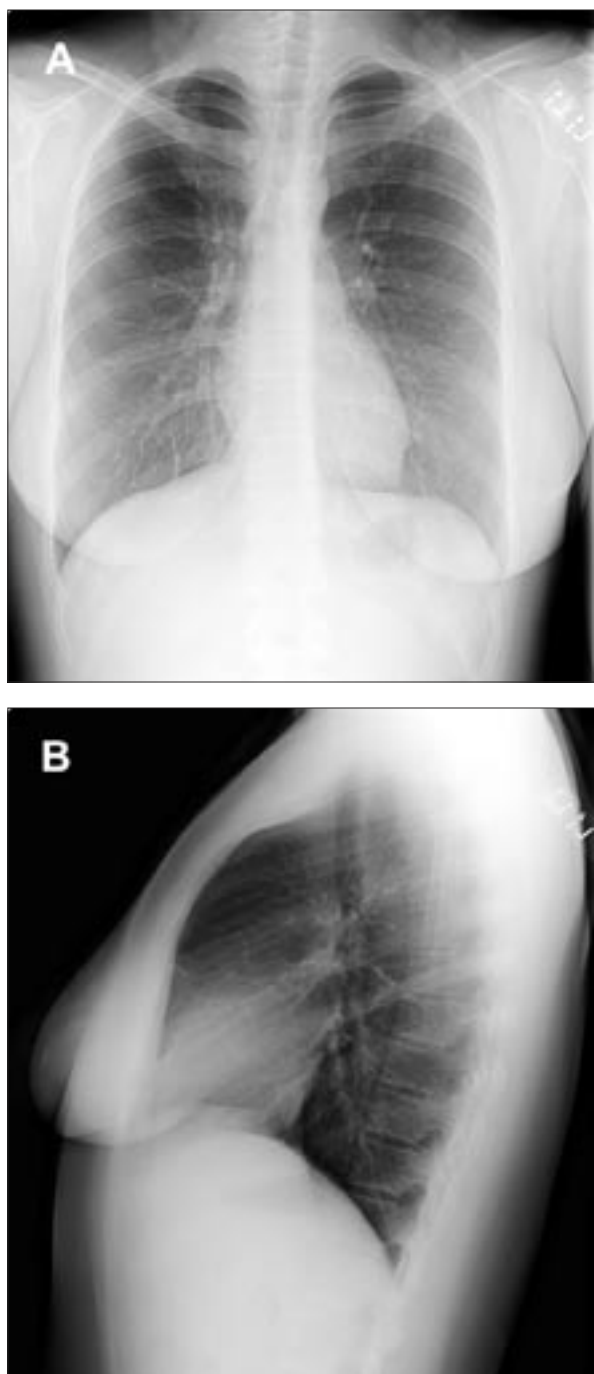
The patient's presentation and biopsy results were most consistent with pulmonary eosinophilia, as opposed to other processes. She was at risk for infection in the set-

**Figure 2.** Chest CT showing diffuse patchy nodular infiltrate in all lung fields with dense consolidation in the lower lobes.



**Figure 3.** Transbronchial biopsy sections showing interstitial and intra-alveolar eosinophilic infiltrates with giant cells and Charcot-Leyden crystals.





**Figure 4.** Chest radiograph at 3-month follow-up showed resolution of the pulmonary infiltrates: PA view (A) and lateral view (B).

ting of immunosuppression on azathioprine and recent infliximab infusion; however, she demonstrated no improvement on antibiotics, and all cultures were negative. With a negative ANCA and no histologic evidence of vasculitis or granulomatous inflammation, Wegener granulomatosis seemed unlikely. Biopsy was also negative

for evidence of bronchopulmonary Crohn's disease: there were no granulomas, interstitial fibrosis, or alveolitis. Additionally, bronchopulmonary Crohn's disease has been reported to be treated in the past with infliximab<sup>4,5</sup> and the patient likely would have improved on this drug therapy. Of note, eosinophilic bronchial infiltrates rarely have been reported in patients with Crohn's disease, but in these reports the patients were asymptomatic and the infiltrates were incidentally discovered.<sup>6,7</sup>

Other etiologies for the patient's pulmonary eosinophilia were excluded. Infectious etiologies were ruled out by negative stool studies for helminthes and negative blood and bronchoalveolar lavage cultures for bacteria and fungi. Though the patient did not undergo serum precipitins assay for aspergillus, her IgE concentration was much less than the 1,000 IU/mL expected for the diagnosis of allergic bronchopulmonary aspergillosis, and her clinical findings were not consistent with this diagnosis. Churg-Strauss syndrome was ruled out based on a negative ANCA serology as well as the TBB histology, which was negative for vasculitis or granuloma formation.

Although asthma can be associated with a peripheral eosinophilia and elevated IgE in connection with atopic tendencies, the patient's symptoms, time course related to infliximab administration, degree of eosinophilia, and TBB results were most consistent with drug-induced pulmonary eosinophilia. Asthma has been associated with idiopathic chronic eosinophilic pneumonia,<sup>8</sup> making this a possible etiology. However, this disease requires a much longer course of corticosteroids for treatment, and frequently relapses on decrease or withdrawal of treatment.<sup>9</sup> Our patient improved on only a short steroid taper and has remained well off infliximab therapy.

Pulmonary eosinophilia has been associated with a variety of medications, most commonly nonsteroidal anti-inflammatory agents. The patient's history was negative for use of these medications. Her sole medications prior to symptom development were infliximab, azathioprine, and montelukast. To our knowledge, azathioprine has not been associated with pulmonary eosinophilia; additionally, the patient's symptoms and radiograph findings resolved and the peripheral eosinophilia improved despite remaining on this treatment. She had also been on montelukast for control of her asthma, which has been associated with pulmonary eosinophilia in at least one case report.<sup>10</sup> That patient's symptoms improved on withdrawal of the medication. Our patient was maintained on montelukast for control of her asthma, making the medication an unlikely culprit in this case. In addition, the association of pulmonary eosinophilia with montelukast is thought to most likely uncover previously undiagnosed Churg-Strauss vasculitis upon withdrawal of steroids,<sup>11,12</sup> and then generally only in patients receiving oral corticosteroids who have

**Table 1.** Pulmonary Function Test Results 2 Months Following Discharge

	Actual	Predicted, %
Total lung capacity	5.59 L	85
Functional residual capacity	2.84 L	83
Residual volume	1.71 L	90
Forced vital capacity	3.88 L	83
FEV1	2.87 L	76
FEV1/Forced vital capacity	74%	–
Single-breath diffusing capacity	21.27 ml/min/mmHg	84

FEV = forced expiratory volume.

recently had a tapering in steroid dosage.<sup>13,14</sup> Although there was a change in this patient's prednisone dosing, the use of this agent was for a brief period of time, there was no evidence of vasculitis on TBB, and there was no change in montelukast therapy throughout her course. Taken together, we believe it is very unlikely that our patient had Churg-Strauss vasculitis.

An eosinophilic reaction has been associated with infliximab infusion in two previous case reports.<sup>15,16</sup> In the first case, the patient developed acute respiratory distress syndrome and pulmonary eosinophilia in relation to readministration of infliximab after a 15-month drug holiday. These symptoms, in conjunction with elevated ATI concentrations, were consistent with a delayed hypersensitivity reaction to infliximab. The patient improved with intravenous methylprednisolone treatment. In the second case, a patient developed an eosinophilic pleural effusion following his second infliximab infusion, which resolved on withdrawal of the infliximab and recurred with rechallenge.

Our patient developed an eosinophilic pneumonia shortly after her third infliximab treatment, responded to treatment for a drug-induced phenomenon, and remained healthy off the offending agent. The most likely diagnosis is drug-induced pulmonary eosinophilia secondary to inf-

liximab. ATI was negative, making a hypersensitivity reaction unlikely. Although eosinophilic reactions have been reported in association with infliximab, to our knowledge, this is the first reported case of isolated pulmonary eosinophilia as a reaction to infliximab therapy.

## Conclusions

Clinicians should consider pulmonary eosinophilia in the differential diagnosis of patients receiving infliximab who develop pulmonary infiltrates with dyspnea.

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# Review

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Despite intense investigation and significant advances in understanding, the underlying etiology of Crohn's disease remains largely unknown. This is in part due to the myriad ways the disease manifests, likely reflecting the complex and heterogeneous nature of its pathogenesis. Clearly, immune dysregulation is present, but to what degree and in what direction (eg, increased inflammation versus impaired regulation of inflammation) is not yet clear. The report by Rubin and colleagues<sup>1</sup> describes the case of a Crohn's patient who developed an additional hyperimmune state during treatment with immunomodulators including infliximab for Crohn's.

Acute eosinophilic pneumonia (AEP) is characterized by the rapid onset of fever, cough, dyspnea, and pulmonary infiltrates. Bronchoalveolar lavage (BAL) showing high percentages of eosinophils strongly supports the diagnosis. It is distinguished from the chronic form of the disease by the acuity of onset, need for only short term (<6 months) steroid treatment, and lack of recurrence after treatment. Although thought to be an acute hypersensitivity response, most cases are idiopathic. Precipitating exposures such as drugs or cigarette smoke are occasionally, but infrequently, found.

The patient in this report had a known diagnosis of asthma, a condition associated with hypereosinophilia. Though asthma is concurrently found in approximately half the cases of chronic eosinophilic pneumonia, it has not been described in acute disease prior to this case.<sup>2</sup> This raises intriguing questions regarding the biology of TNF blockade, Crohn's disease, and AEP. High levels of IL-5, a Th-2 secreted cytokine involved in eosinophil growth and regulation, have been found in BAL fluid from AEP.<sup>3,4</sup> Infliximab targets Th-1 regulated diseases such as Crohn's and has been postulated to shift the balance of Th cell activity toward Th-2 phenotypes.<sup>5</sup> Pharmacologic suppression of one arm may thus alter the delicate balance of Th cells and create an opportunity for hyperactivity of the other arm.

This case underscores the need for further investigation into the immune biology of inflammatory processes, including Crohn's disease. As we manipulate the immune system with newer, more potent biologic therapies, we must also assess the impact of those manipulations on the immune system's ability to maintain homeostasis among its different components.

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