

Clinical Communication

Eosinophilic pulmonary complications of dupilumab in 2 patients with asthma and chronic rhinosinusitis with nasal polyps

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Clinical Implications

Two cases are presented that demonstrate that dupilumab may be associated with serious pulmonary complications related to eosinophilic infiltration of the tracheobronchial tree and lung parenchyma. Careful monitoring of symptoms and eosinophil counts allows for early detection and initiation of treatment to prevent adverse clinical outcomes.

Severe asthma is a heterogeneous clinical entity composed of multiple different phenotypes. Many patients with moderate to severe asthma have an inflammatory endotype characterized by high levels of T_H2 -mediated inflammation and elevated levels of IL-4, IL-5, and IL-13¹ as well as significant peripheral and airway eosinophilia. These patients frequently require treatment with tiotropium, azithromycin, or chronic oral corticosteroids, which can be associated with various long-term side effects.

The development of mAbs specifically targeting these pathways has dramatically changed the care of these patients. In clinical trials, the anti-IL-4/IL-13 mAb dupilumab decreased exacerbation frequency and severity, improved lung function and symptoms, and reduced oral corticosteroid use.²⁻⁴

Although transient peripheral eosinophilia has been reported in patients with asthma and chronic rhinosinusitis with nasal polyps treated with dupilumab, significant hypereosinophilia and pulmonary complications are much rarer, having occurred in only 4 patients (0.2%) in the phase 3 LIBERTY ASTHMA QUEST trial.² We report 2 patients with severe asthma and chronic rhinosinusitis with nasal polyps with refractory sinonasal symptoms and/or deteriorating lung function who developed significant pulmonary eosinophilic complications following initiation of dupilumab.

The first patient, a 51-year-old woman, had been started on mepolizumab several years earlier for severe asthma requiring multiple courses of oral steroids despite high-dose mometasone-formoterol twice daily. After 4 years of adequate control with mepolizumab, her symptoms began to worsen and her FEV₁ had decreased from 1.75 L (61% predicted) to 1.36 L (47%). Her mometasone/formoterol was increased to 4 to 8 puffs daily, and she was started on tiotropium. After 8 months, her FEV₁ had improved to 1.80 L (63%), but she continued to experience bothersome nocturnal symptoms and a chronic productive cough with no significant abnormality on chest x-ray, so her mepolizumab was switched to biweekly dupilumab. Four months later, despite an increase in her FEV₁ to 2.39 L (81%), she reported a persistent productive cough and only mildly improved dyspnea, which did not resolve with a course of azithromycin. In addition,

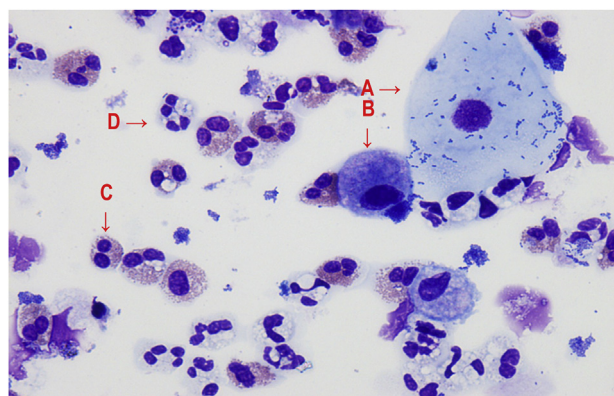


FIGURE 1. Induced sputum showing multiple eosinophils suggestive of the diagnosis of eosinophilic bronchitis. (A) Mouth epithelial cell, (B) macrophage, (C) eosinophil, and (D) neutrophil.

her blood eosinophils had increased to $760 \times 10^6/L$ from a baseline of $270 \times 10^6/L$ and her fractional exhaled nitric oxide was elevated at 93 parts per billion. Sputum induction showed sputum eosinophils of 60% (Figure 1), and a diagnosis of eosinophilic bronchitis was made on the basis of the presence of excessive sputum eosinophilia despite improved spirometry. Dupilumab was stopped, and she was started on prednisone 50 mg daily with significant symptomatic improvement.

The second patient, a 58-year-old woman with severe asthma and chronic rhinosinusitis with nasal polyps who had required 4 courses of oral corticosteroids in the previous year, was started on dupilumab for uncontrolled symptoms despite regular use of both high-dose fluticasone/vilanterol and fluticasone furoate. Her symptoms improved dramatically, and she was able to significantly diminish her rescue inhaler use. However, following her seventh dose of dupilumab, she developed diffuse arthralgias, worsening dyspnea, and nasal congestion for which she was prescribed prednisone 25 mg daily. Her symptoms persisted despite prednisone, so she presented to the emergency room where she was found to have a peripheral eosinophil count of $24,600 \times 10^6/L$ from a baseline of $200 \times 10^6/L$. A computed tomography scan of the chest showed bilateral, patchy, predominantly peripheral areas of consolidation with volume loss (Figure 2). Serologic testing for common parasitic infections, anti-neutrophil cytoplasmic antibodies, connective tissue disease serology, and a myositis panel were all negative, so she was diagnosed with chronic eosinophilic pneumonia. She refused bronchoscopy, so dupilumab was stopped and prednisone was increased to 60 mg daily. Four months later, her symptoms had improved dramatically, her chest x-ray showed near-complete resolution of the previously seen infiltrates, and her peripheral eosinophil count had fallen to $510 \times 10^6/L$.

Both cases are unique in that they represent the first reported case, to our knowledge, of eosinophilic bronchitis and the highest reported eosinophil count seen in association with dupilumab, respectively. The exact mechanisms underlying dupilumab-induced hypereosinophilia remain unclear. IL-4/IL-13 signaling via IL-4R α results in increased secretion of chemokines, namely

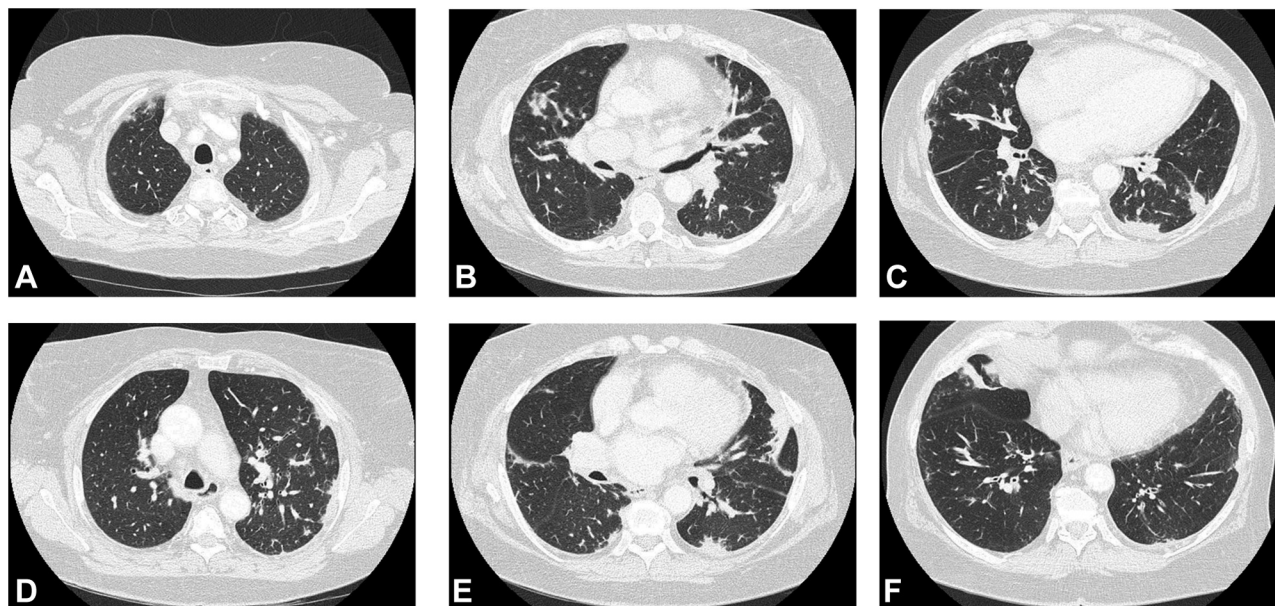


FIGURE 2. (A-F) Computed tomography scans of the chest (1-mm thickness) demonstrating bilateral patchy peripheral infiltrates and atelectasis suggestive of chronic eosinophilic pneumonia.

the C-C type chemokines 11, 26, and 13, which bind to CCR3 on eosinophils, resulting in eosinophil migration into peripheral tissues.⁵ Although it is currently thought that the hyper-eosinophilia seen with dupilumab is merely an epiphenomenon resulting from blockage of this signaling cascade, the present cases call this idea into question because in both cases there was evident eosinophil migration into the airways and pulmonary parenchyma. It also remains a possibility that the withdrawal of oral glucocorticoids facilitated by dupilumab may unmask previously suppressed eosinophilic diseases, such as eosinophilic granulomatosis with polyangiitis, in some patients. However, this seems unlikely in the present cases because neither patient had a history of autoimmune disease and both were only intermittently on oral glucocorticoids.

With multiple cases of chronic eosinophilic pneumonia now being reported in the literature,⁶⁻⁹ it seems increasingly likely that a causal relationship with dupilumab exists, although the exact mechanisms remain unknown. There are certainly weaknesses in both cases, namely the lack of a baseline sputum eosinophil count and fractional exhaled nitric oxide in one and absence of bronchoscopically confirmed eosinophilic pneumonia in the other. Nonetheless, we believe that the temporal relationship between introduction of dupilumab and development of eosinophilic pulmonary complications, as well as the improvement with drug withdrawal, is clear evidence that these complications were due to dupilumab.

There are likely unidentified patient and immune-related factors that influence the development, degree, and site of hypereosinophilia following dupilumab administration, but further research is needed to clarify their exact nature. Both of our patients responded well to prompt withdrawal of dupilumab initiation of oral corticosteroids, but it remains unclear whether they should ever be rechallenged with dupilumab or other biologics because the risk of recurrent eosinophilic pneumonia is unknown.

It is important that clinicians be aware of the potential for serious eosinophilic complications in patients on dupilumab and engage in regular monitoring for new or worsening peripheral eosinophilia. There should be a low threshold to obtain additional imaging if a patient's respiratory symptoms suddenly worsen, especially if associated with significant hypereosinophilia. Prompt initiation of appropriate therapy seems to result in rapid clinical resolution, but increased awareness is imperative to minimize delays in diagnosis and treatment.

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