Received: 11 April 2023 | Accepted: 29 June 2023

DOI: 10.1002/rcr2.1192

CASE REPORT

Respirology Case Reports OPEN ACCESS APSR WILEY

Eosinophilic pneumonia developed after dupilumab administration in a patient with atopic dermatitis

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Associate Editor: Kazuyuki Nakagome

Abstract

A 63-year-old woman with refractory atopic dermatitis started treatment with dupilumab. She developed a cough 4 days later, sputum, and a slight fever 2 weeks later. Laboratory test results showed a blood eosinophil count of 7360/μL. Chest x-ray and computed tomography scan showed infiltrative shadows with surrounding consolidation of both upper lobes. Bronchoalveolar lavage fluid eosinophil count was increased (50.0%), and histopathological findings were consistent with numerous eosinophilic infiltrations. Treatment with prednisolone 30 mg/day (0.5 mg/kg/day) was initiated. Her symptom resolved, and the shadow of the lung fields improved. There have been no reported cases of eosinophilic pneumonia diagnosed 7 weeks after the administration of dupilumab for atopic dermatitis.

KEYWORDS
atopic dermatitis, dupilumab, eosinophilic pneumonia, IL-4/13

INTRODUCTION

Dupilumab is a monoclonal antibody that specifically binds to the interleukin (IL)-4/13 receptor.[1] In the past literature, there have been a few reports of eosinophilic pneumonia as a side effect of dupilumab. We experienced a case of eosinophilic pneumonia in a patient with atopic dermatitis, which developed after dupilumab administration.

CASE REPORT

A 63-year-old woman diagnosed with atopic dermatitis had regularly attended the dermatology department of our hospital. She had been receiving budesonide for comorbid cough variant asthma for 10 years with controlled cough symptoms. However, she had no history of paediatric or typical asthma, chronic sinusitis, other allergic diseases, or prolonged cough after upper respiratory infections. Despite receiving antihistamines and steroid ointment administration, her skin condition did not improve, thus dupilumab was added for refractory atopic dermatitis in November of a certain year. She developed a cough 4 days later, sputum, and a slight fever 2 weeks later. A baseline blood eosinophil count of 610/μL increased to 1770/μL after 2 weeks and then continued to increase (Figure 1). Based on the diagnosis of worsened cough variant asthma, a nearby doctor changed budesonide to budesonide/formoterol. However, the symptoms did not improve, and the patient refused to receive dupilumab after the second dosing. In January of the following year, she visited the respiratory medicine department for an investigation. A physical examination revealed a body temperature of 37.7°C, and coarse crackles were heard in both upper lungs. There was no high-grade fever, numbness, or weakness suggestive of vasculitis. Laboratory test results on admission showed a blood eosinophil count of 7360/μL, C-reactive protein (CRP) of 3.56 mg/dL, total serum IgE of 2.4 IU/mL, and myeloperoxidase anti-neutrophil cytoplasmic antibody (MPO-ANCA) of negative (Figure 1). Specific IgE antibodies to 16 common inhalant allergens were negative.

Despite normal radiological findings prior to the dupilumab dosing, chest x-ray and CT scan showed infiltrative shadows with surrounding consolidation of both upper lobes (Figure 2), and antibiotics were ineffective. On the 4th day after hospitalization, a bronchoscopy was performed, followed by bronchoalveolar lavage (BAL) and transbronchial lung biopsy. The BAL eosinophil count was

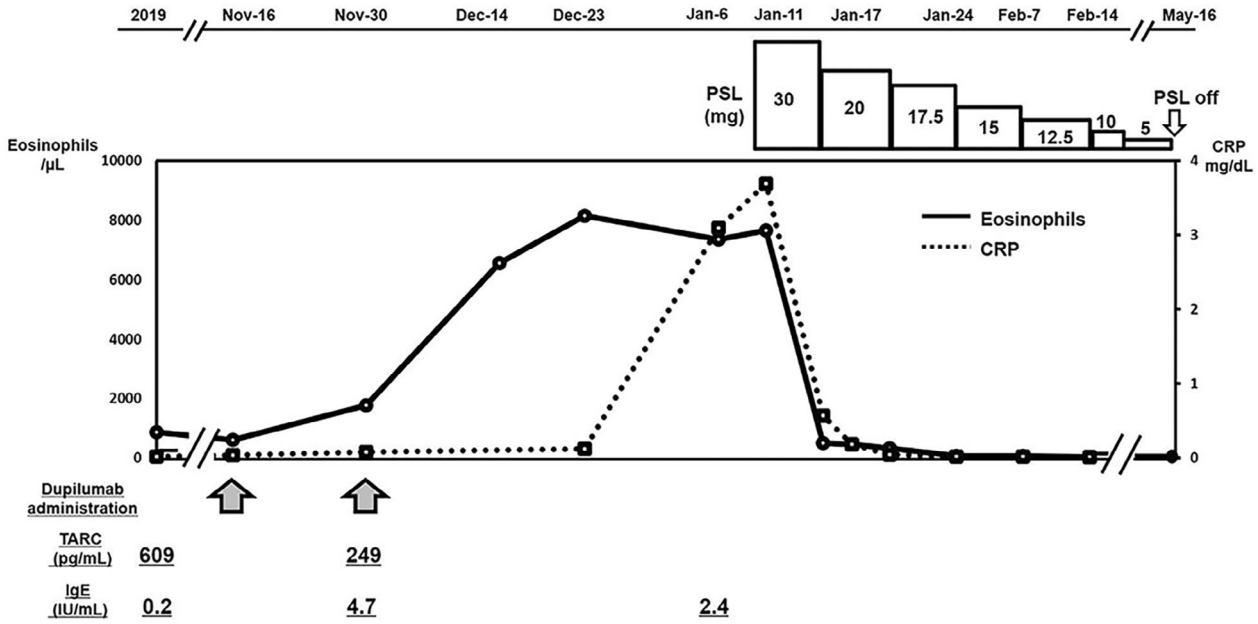

FIGURE 1 Changes in type-2/eosinophilic biomarkers before and after dupilumab treatment. CRP, C-reactive protein; TARC, thymus and activation-regulated chemokine.

remarkably increased (50.0%). Histopathological findings were consistent with numerous eosinophilic infiltration (Figure 1). Treatment with prednisolone 30 mg/day (0.5 mg/kg/day) was initiated. Changes in type-2/eosinophilic biomarkers are shown in Figure 1. After the start of prednisolone treatment, her symptoms resolved, the shadow of the lung fields improved, and her blood eosinophil count decreased to 490/μL 3 days after the prednisolone administration. Prednisolone dose was tapered over approximately 1–2 weeks and finished 124 days after starting treatment. No recurrence was observed after that.

DISCUSSION

Dupilumab is a monoclonal antibody against the human IL-4/13 receptor. It specifically binds to the IL-4 receptor alpha subunit, which is common to both the IL-4 and IL-13 receptor complex, and inhibits IL-4 and IL-13 signalling, thereby broadly suppressing type 2 inflammatory responses. It is effective against treatment-resistant bronchial asthma, atopic dermatitis, and chronic rhinosinusitis in patients with nasal polyps.[1,2]

In a previous phase 3 clinical trial, approximately 0.16% (2/1263) of adult patients with moderate-to-severe uncontrolled asthma developed severe eosinophilic pneumonia and discontinuation of dupilumab.[1] Nishiyama et al. measured the serum cytokine levels in two cases of dupilumab-associated eosinophilic pneumonia and found elevated IL-5, but not in patients who did not develop dupilumab-associated eosinophilic pneumonia.[3] Kurihara et al. reported two similar cases with high-grade eosinophilia and emphasized fever and dyspnea as initial symptoms of eosinophilic pneumonia.[4] Eger et al. described four oral corticosteroid (OCS)-dependent asthma patients in whom IL-5 pathway biologics were switched to dupilumab leading to the development of eosinophilic pneumonia in one patient.[5] These findings suggest that not only mild eosinophilia caused by IL-4/13 blocking but also severe eosinophilia caused by IL-5 might be associated with the development of eosinophilic pneumonia. Inappropriate distribution of eosinophils due to blocked IL-4 and IL-13 seems to be a likely mechanism in this case. However, the origin of IL-5 or the relationship between blood eosinophilia and pulmonary eosinophilic infiltration is still unknown. Further studies are needed to clarify these.

Eger et al. hypothesized that the OCS-dependent severe asthma patient who developed eosinophilic pneumonia with hypereosinophilia after switching to dupilumab might originally have had a latent ANCA-negative eosinophilic granulomatosis with polyangiitis (EGPA).[5] This patient did not have severe asthma nor require OCS before dupilumab treatment. In addition, this patient had neither peripheral neuropathy, sinusitis, renal lesion, gastrointestinal lesions, nor other skin lesions than atopic dermatitis. Kurihara's two cases also had a similar degree of fever to this patient. However, we cannot exclude ANCA-negative EGPA or its prestage, entirely. Drug-induced eosinophilic pneumonia, other than dupilumab's pharmacological effect, was also possible. However, we did not examine the immunological test such as DLST. Taken together, we think it is difficult to give a definitive interpretation of the mechanisms of eosinophilic pneumonia of this case.

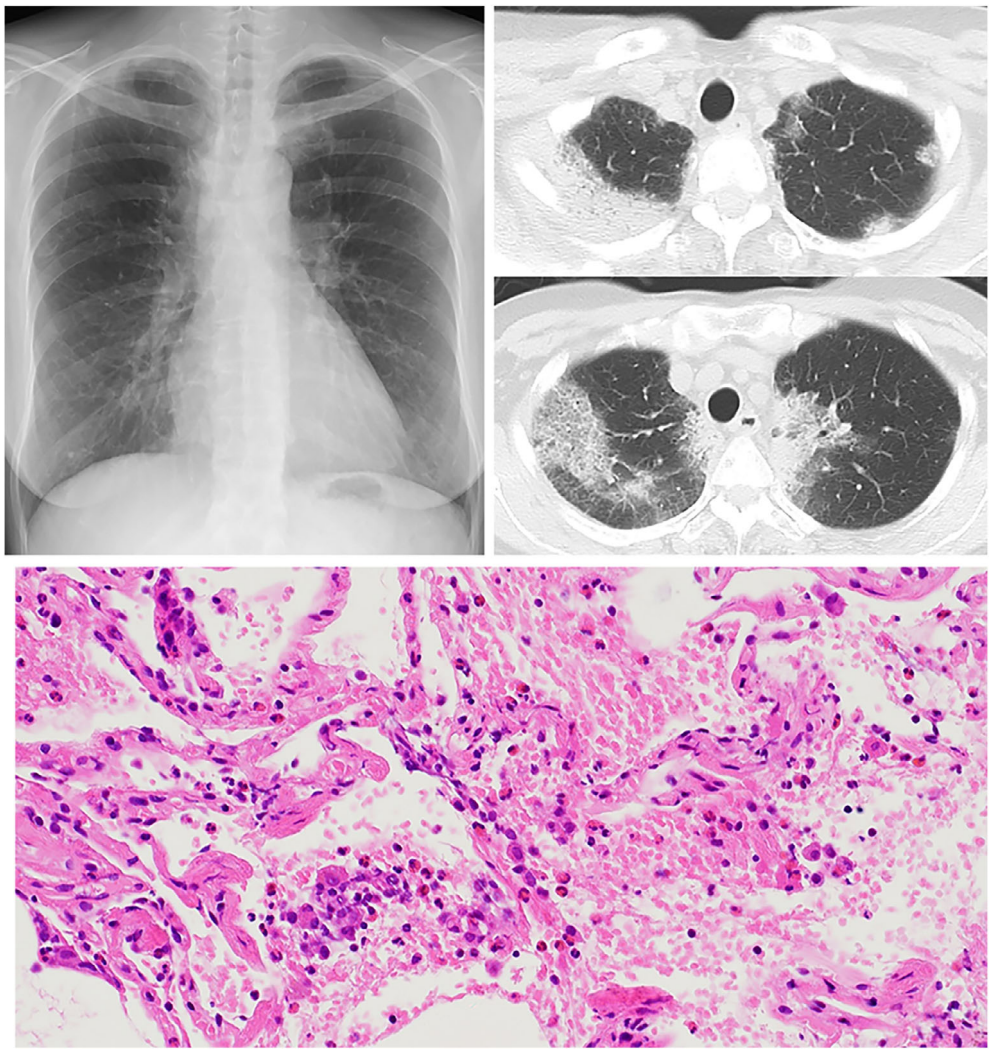

FIGURE 2 Chest x-ray and computed tomography (CT) scan showing infiltrative shadows with surrounding consolidation of both upper lobes (upper panel) and histopathological examination findings of numerous eosinophilic infiltration (lower panel). (HE staining × 200).

In the past literature, there have been a few reports of eosinophilic pneumonia after the administration of dupilumab. However, there have been no reported cases of eosinophilic pneumonia diagnosed 7 weeks after the administration of dupilumab for atopic dermatitis. The absence of respiratory symptoms before dupilumab treatment may have contributed to the early discontinuation of the treatment. However, it still took more than a month to be diagnosed since symptoms developed, suggesting a delay in diagnosis. Therefore, eosinophilic pneumonia should be considered as a differential diagnosis in the presentation of fever or dyspnea after dupilumab administration for atopic dermatitis.

CONFLICT OF INTEREST STATEMENT

None declared.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The authors declare that appropriate written informed consent was obtained for the publication of this manuscript and accompanying images.

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How to cite this article: Kanata K, Shirai T, Ichijo K, Uehara M. Eosinophilic pneumonia developed after dupilumab administration in a patient with atopic dermatitis. Respirology Case Reports. 2023;11:e01192. https://doi.org/10.1002/rcr2.1192