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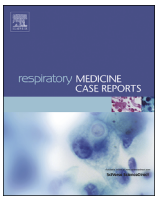

Case Report

A case of recurrent chronic eosinophilic pneumonia after switching from benralizumab to dupilumab

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ABSTRACT

Dupilumab inhibits interleukin-4Rα and suppresses type 2 inflammation. Careful administration of dupilumab is required because it increases the blood eosinophil count secondary to a decrease in local eosinophil counts, sometimes resulting in eosinophilic complications. We herein report a case of recurrent chronic eosinophilic pneumonia after switching from benralizumab to dupilumab. A 54-year-old man with a history of eosinophilic pneumonia presented to our hospital with symptoms of cough, fever, and phlegm production six months after beginning dupilumab administration for recurrent chronic rhinosinusitis. When using dupilumab, it is essential to carefully monitor patients' eosinophil trends and pulmonary symptoms.

1. Introduction

Eosinophilic pneumonia is a rare disease characterized by marked accumulations of infiltrating eosinophils in the alveolar spaces and interstitium [1]. Dupilumab-induced eosinophilic pneumonia has recently become problematic in some patients. We herein present a case of recurrent chronic eosinophilic pneumonia (CEP) in a 54-year-old man 6 months after switching from benralizumab to dupilumab.

2. Case presentation

A 54-year-old man presented with symptoms of cough, fever (37.8 °C), and phlegm production. His symptoms did not improve after 6 days of amoxicillin (250 mg/day) and clavulanate (125 mg/day); therefore, he was referred for assessment by a respiratory physician and admitted to our hospital for examination and treatment. His medical history was significant for eosinophilic chronic rhinosinusitis (for which he had undergone two endoscopic sinus surgeries), bronchial asthma, eosinophilic otitis media, and hospitalization for eosinophilic pneumonia. He had been using benralizumab to manage his bronchial asthma for 4 months. However, he switched to dupilumab 6 months before presentation because his nasal symptoms had worsened. He was allergic to carbocisteine and did not smoke. His blood pressure was 108/64 mmHg, pulse rate was 64 beats/min, body temperature was 36.4 °C, and arterial oxygen saturation was 95 % on room air. Chest auscultation revealed no pulmonary murmurs or wheezing. Pulmonary function testing showed that his forced expiratory volume in 1 second was 3.47 L, percent predicted forced expiratory volume in 1 second was 102.0 %, and fractional exhaled nitric oxide was 30 ppb. Blood tests revealed a white blood cell count of 11,000/μL (reference range, 3900–9800/μL) (neutrophils, 54.9 %; lymphocytes, 8.2 %; eosinophils, 30.6 %; monocytes, 5.9 %), *C*-reactive protein concentration of 12.6 mg/dL (< 0.3 mg/dL), PR3-antineutrophil cytoplasmic antibody (PR3-ANCA) and MPO-ANCA were negative. The patient's to-

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tal IgE concentration was 349 IU/mL (reference range, <170 mg/dL), and he had a positive radioallergosorbent test for orchard grass, Japanese cedar, cypress, *Aspergillus*, *Alternaria*, and moth. Chest X-ray examination showed a ground-glass opacity in the right upper lobe, and chest computed tomography showed right upper lobe consolidation with bronchial wall thickening and air bronchograms (Fig. 1). After admission, bronchoalveolar lavage fluid (BALF) was obtained from the right B1b segment by bronchoscopy. We instilled 200 mL of 0.9 % sodium chloride and aspirated 99 mL of fluid containing 62 % eosinophils, 0 % neutrophils, 2 % lymphocytes, 0 % monocytes, and 1 % basophils with a CD4/8 ratio of 3.22. A transbronchial lung biopsy showed infiltration of eosinophils and no evidence of fungal infection or vasculitis (Fig. 2). After admission, oral prednisolone (30 mg/day) was started according to the rapid BALF analysis results. The oral steroid therapy resulted in improvement in the patient's respiratory symptoms and a dramatic decrease in his blood eosinophil count. The patient was discharged on the 16th hospital day, and his systemic steroid therapy was tapered to 5 mg/day after 3 months of outpatient care.

Fig. 3 shows the patient's clinical course and the changes in his systemic steroid dose (mg/day) and serum eosinophil concentration (%). The systemic steroid dose was reduced in 1-mg increments from 5 mg/day according to the improvement in the patient's rhinosinusitis symptoms after dupilumab administration. Pulmonary symptoms developed 6 months after beginning dupilumab administration, when the oral prednisolone had decreased to 2 mg/day. The serum eosinophil concentration gradually increased and peaked at near 40 % on admission day 3.

3. Discussion

Eosinophilic pneumonia is characterized by an increase in the eosinophil concentration within lung tissue or BALF [2]. Idiopathic localized eosinophilic pneumonia is classified into acute eosinophilic pneumonia and CEP depending on its progression [3]. CEP is a rare disease and more common in non-tropical regions with a low prevalence of parasitic infection. In contrast to patients with acute eosinophilic pneumonia, most patients with CEP are nonsmokers (<10 %) and have a history of allergic symptoms including asthma (as many as two-thirds of patients), atopy (approximately half of patients), eczema, urticaria, and nasal polyposis [4]. The diagnostic criteria for CEP include a characteristic clinical presentation including cough, dyspnea, and fever lasting >2 weeks; abnormal chest

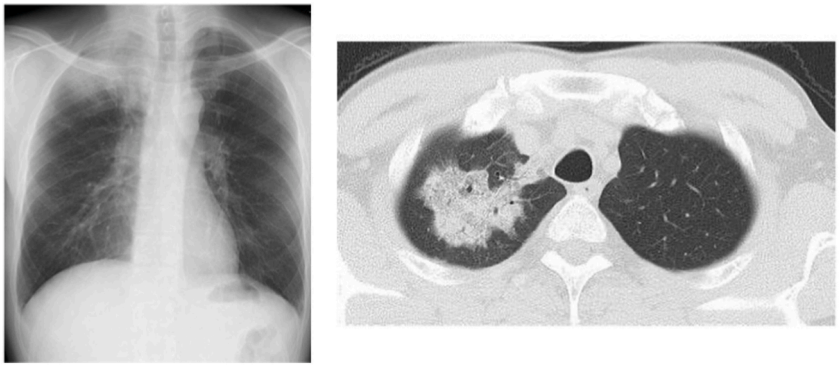

Fig. 1. Chest X-ray and computed tomography images
Chest X-ray examination revealed a ground-glass opacity in the right upper lobe, and chest computed tomography showed right upper lobe consolidation with bronchial wall thickening and air bronchograms.

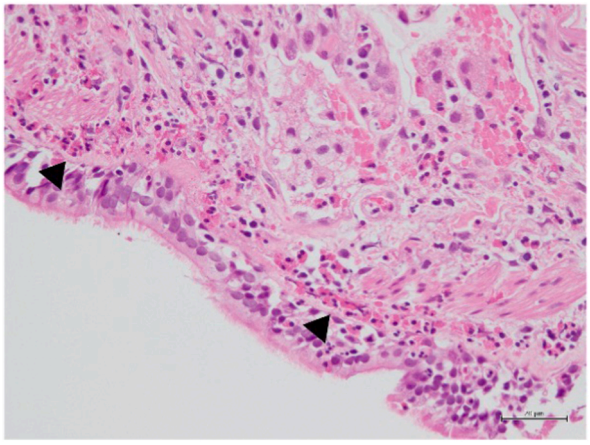

Fig. 2. Histologic image of transbronchial lung biopsy specimen
Histologic examination showed eosinophilic infiltration (black arrow) in the submucosal tissue.

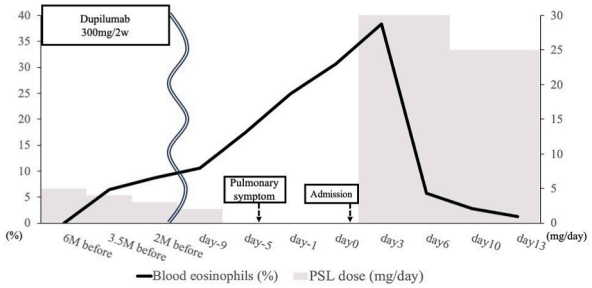

Fig. 3. Patient's clinical course
This graph shows the blood eosinophil count and prednisolone dose. The solid line indicates the blood eosinophil count, and the bar graph indicates the prednisolone dose (mg/day).

Table 1
Previously published case reports of eosinophilic pneumonia caused by dupilumab.

Case	Author	Age	Sex	Race	Smoke	Symptom	Side	Since dupilumab	Treatment
1	Menzella et al. [10]	56	M	Caucasian	No	Fever	Both	5M	PSL 50mg/day
2	Nishiyama et al. [11]	37	F	East asian	No	Dry cough, Dyspnea, Low-grade fever	Both	5M	PSL 30mg/day
3	Nishiyama et al. [11]	40	F	East asian	Ex	Dyspnea, Chest pain, High fever	Both	3M	PSL 30mg/day
4	Nishida et al. [12]	72	F	East asian	No	Cough, Dyspnea, Loss of appetite	Both	7M	PSL 40mg/day
5	Kurihara et al. [7]	55	F	East asian	No	Fever, Dyspnea	Both	5W	PSL 50mg/day
6	Kurihara et al. [7]	59	M	East asian	No	Fever, Fatigue, Dyspnea	Both	11W	PSL 0.5mg/kg/day

radiographic findings; BALF eosinophilia (usually >25 %), blood eosinophilia, and/or evident eosinophil infiltration in the lungs; and exclusion of other types of eosinophilic pneumonia such as eosinophilic granulomatosis with polyangiitis (EGPA) [1]. Our patient not only had a history of CEP but also showed right upper lobe consolidation on chest computed tomography, 62 % eosinophils in the BALF, eosinophilic infiltration on transbronchial lung biopsy, without ANCA positivity or vasculitis. Therefore, he was clinically considered to have developed recurrence of CEP. It is difficult to rule out the possibility of EGPA generally. We need to pay attention to the appearance of vasculitis and other symptoms. The diagnosis of EGPA should be based on objective evidence of vasculitis like histopathological findings according to the most recent guidelines [5].

Dupilumab is a humanized IgG4 monoclonal antibody that suppresses type 2 inflammation in conditions such as intractable eosinophilic chronic rhinosinusitis, bronchial asthma, and atopic dermatitis and an excellent treatment option currently available for the modern biologic treatment of severe asthma and CRSwNP [6]. Dupilumab inhibits the expression of vascular cell adhesion molecule-1 and the production of eotaxin via interleukin (IL)-4 and IL-13 [7]. This molecular mechanism inhibits eosinophilic migration in tissues. Group 2 innate lymphoid cells might produce high amounts of IL-5 by the action of alarmins (e.g., thymic stromal lymphopoietin, IL-25, IL-33) via a mechanism that is independent of IL-4 and IL-13 regulation [8]. The IL-5 concentration is reportedly increased in the BALF of patients with eosinophilic pneumonia [9]. Additionally, eosinophils are continuously generated in bone marrow stimulated by IL-5, resulting in hypereosinophilia. Furthermore, tapering of corticosteroid therapy also contributes to this condition. In patients with dupilumab-induced eosinophilic pneumonia, eosinophils are thought to excessively migrate to the lung tissue.

In the present case, the patient received benralizumab (an IL-5Rαa inhibitor), which suppressed eosinophil production from the bone marrow and decreased the blood eosinophil concentration to almost 0 %. However, the blood eosinophil concentration then increased after switching from benralizumab to dupilumab; this was followed by the development of respiratory symptoms despite careful tapering of prednisolone in 1-mg increments. Patients with a history of eosinophilic pneumonia require stricter management when receiving dupilumab.

We identified six previously reported cases of dupilumab-induced eosinophilic pneumonia (Table 1). The patients' ages ranged from 37 to 72 years, and none of the patients were current smokers. For patients with mild CEP, 40–60 mg of oral prednisolone may be sufficient initial therapy [2]. All patients described in previous case reports received appropriate oral prednisolone doses and achieved remission. Time to eosinophilic pneumonia ranged from 5 weeks to 7 months after initiation of dupilumab. The TRAVERSE study showed an increase in the blood eosinophil concentration after 4 weeks, but the concentration returned to baseline by 96 weeks [13]. In our case, the patient developed respiratory symptoms 6 months after dupilumab administration. Long-term follow-up is considered necessary because the eosinophil elevation is suppressed when systemic steroids are used.

4. Conclusion

We experienced a case of eosinophilic pneumonia despite careful tapering of systemic steroids 6 months after switching from benralizumab to dupilumab. Patients with a history of eosinophilic pneumonia require stricter management when receiving dupilumab.

Ethics statement

This study followed the principles of the Helsinki Declaration. The patient provided informed consent about publication of the case report.

Author contributions

DN and EM designed the study and wrote the manuscript. All authors approved the final version of the manuscript.

Declaration of competing interest

The authors have no conflicts of interest.

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