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CASE SERIES

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Feasibility of continued treatment with dupilumab in patients with type 2 inflammatory disease who developed eosinophilic pneumonia: 3 case reports

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Abstract

Several reports have described dupilumab-induced eosinophilic pneumonia (EP) after treatment with dupilumab in patients with type 2 inflammatory disease. Other reports have suggested the efficacy of dupilumab for chronic EP (CEP). Whether dupilumab can be continued in patients with type 2 inflammatory disease who develop EP during dupilumab treatment remains unclear. We present herein three cases with different clinical presentations involving dupilumab and EP. In Case 1, dupilumab was discontinued because of dupilumab-induced EP during the treatment of asthma. In Case 2, although pre-existing idiopathic EP worsened during the treatment of eosinophilic chronic rhinosinusitis (ECRS), dupilumab was continued. In Case 3, CEP and ECRS were successfully treated with dupilumab and corticosteroids were discontinued. In conclusion, treatment with dupilumab in patients with type 2 inflammatory disease and idiopathic EP is worth considering if the benefits are deemed to outweigh the risks and careful attention is given to the clinical course.

KEYWORDS

asthma, dupilumab, eosinophilic chronic rhinosinusitis, eosinophilic pneumonia

INTRODUCTION

Dupilumab is a monoclonal antibody effective against type 2 inflammatory diseases such as asthma, eosinophilic chronic rhinosinusitis (ECRS), and atopic dermatitis (AD), by blocking the interleukin (IL)-4/IL-13 pathway.[1] However, several reports have described dupilumab-induced eosinophilic pneumonia (EP) after treatment with dupilumab (Table 1).[2–9] In most of those reports, dupilumab was discontinued and the patients were treated using prednisolone. Other reports have described the efficacy of dupilumab for chronic EP (CEP).[10,11] The pharmacological actions of dupilumab are thought to suppress the accumulation of eosinophils from blood vessels to organs.[1,12] However, consensus remains lacking on whether dupilumab should be continued in patients with asthma, ECRS, or atopic dermatitis who develop EP during dupilumab treatment.

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Case 1

A 77-year-old woman with refractory asthma visited the emergency department and received oral corticosteroid every month, although she was also receiving high-dose inhaled steroids, long-acting bronchodilators, and leukotriene antagonists. She had developed asthma at 59 years old. She was a never-smoker and had no history of AD, allergic bronchopulmonary mycosis (ABPM), EP, ECRS, or eosinophilic granulomatosis with polyangiitis (EGPA). Asthma control test (ACT) score was 8, and respiratory function testing showed a forced expiratory volume in 1 s (FEV_1) of 1.5 L. Biomarkers of type 2 inflammation were as follows: immunoglobulin (Ig)E, 491 IU/mL (normal, < 361 IU/mL); peripheral blood eosinophils, 620/μL; and fractional exhaled nitric oxide (FeNO), 32 ppb. Antigen-specific serum IgE

TABLE 1 Summary of cases of dupilumab-induced eosinophilic pneumonia (EP) during treatment of type 2 inflammatory disease.

Case	Authors	Age (y)/ sex	Target diseases	Type 2 inflammatory comorbidities	Eosinophils, baseline/ onset of EP (μL)	Time from administration of dupilumab to diagnosis of EP[a]	Therapeutic agents for EP	Resumption of dupilumab[b]	Comments
1	Nakashima et al.	54 M	Asthma	ECRS, EOM, EP	NA/3366	6 months	PSL	No	EP developed after changing from benralizumab to dupilumab
2	Zhou et al.	71 M	AD	NA	NA[c]	6 days	PSL	Yes	
3	Frohlich et al.	58 F	Asthma, CRSwNP	NA	200/24,600	>3 months	PSL	No	BAL not performed
4	Kanata et al.	63 F	AD	Cough-variant asthma	610/7360	2 months	PSL	No	
5	Kurihara et al.	55 F	ECRS	Asthma, EOM	NA/3852	9 weeks	PSL	No	Benralizumab started after treatment of dupilumab-induced EP
6	Kurihara et al.	59 F	ECRS	NA	NA/4849	6 months	PSL	No	BAL not performed, EP relapsed after discontinuing PSL
7	Nishiyama et al.	37 F	Asthma, ECRS	AR	276/9040	5 months	PSL	No	EP developed after changing from benralizumab to dupilumab
8	Nishiyama et al.	40 F	Asthma, ECRS	AR	520/5150	3 months	PSL	No	
9	Sudo et al.	65 F	ECRS	NA	NA	>10 weeks	PSL	yes	PSL also used when resuming dupilumab
10	Menzella et al.	56 M	Asthma	CRSwNP	660/2020	5 months	PSL	No	Patient enrolled in a phase III RCT of dupilumab

Note: Except for Case 1, dupilumab was not administered to patients with a history of EP. Most authors discontinued dupilumab when the patient developed dupilumab-induced EP.

Abbreviations: AD, atopic dermatitis; AR, allergic rhinitis; CRSwNP, chronic rhinosinusitis with nasal polyps; ECRS, eosinophilic chronic rhinosinusitis; EOM, eosinophilic otitis media; F, female; M, male; NA, not applicable; PSL, prednisolone; RCT, randomized controlled trial.

[a]The time of EP diagnosis was defined as the time EP was confirmed by findings from laboratory tests, computed tomography, or bronchoalveolar lavage (BAL) fluid.

[b]Resumption of dupilumab was defined as clearly documented in the case report.

[c]Figure in the case report roughly states 500–1000 μL.

was positive for mites, *Aspergillus*, and house dust. She was started on subcutaneous dupilumab every 2 weeks as additional therapy (Figure 1). On day 24 of dupilumab treatment, she developed fever and headache. The peripheral blood eosinophil count increased to 9646/μL. Chest radiographs showed infiltrative shadows in the right lower lung fields (Figure 1C). Computed tomography (CT) of the chest showed non-regional consolidation, ground-glass opacity, and contractile changes in the right lower lobe (Figure 1A,B). Bronchoscopy was not performed because the patient declined consent. We diagnosed dupilumab-induced EP, as findings suggestive of infection (e.g., purulent sputum), history of new medications other than dupilumab, or environmental changes suggestive of hypersensitivity pneumonitis were not present. She was followed-up without corticosteroids, but symptoms remained unimproved. On Day 29, the peripheral blood eosinophil count increased further to 14,101/μL. Dupilumab was discontinued and prednisolone was started at 30 mg/day. After prednisolone administration, subjective symptoms and chest image findings rapidly improved and prednisolone was tapered. On Day 50, benralizumab was started while prednisolone continued to be tapered off. On Day 106, prednisolone was finally discontinued. No relapse of EP had been seen as of 38 months after PSL discontinuation. Symptoms of asthma had also improved and ACT score remained above 20.

Case 2

A 50-year-old woman presented to the outpatient clinic for treatment of asthma. She was a former smoker and had developed asthma at 40 years old. Her medical history

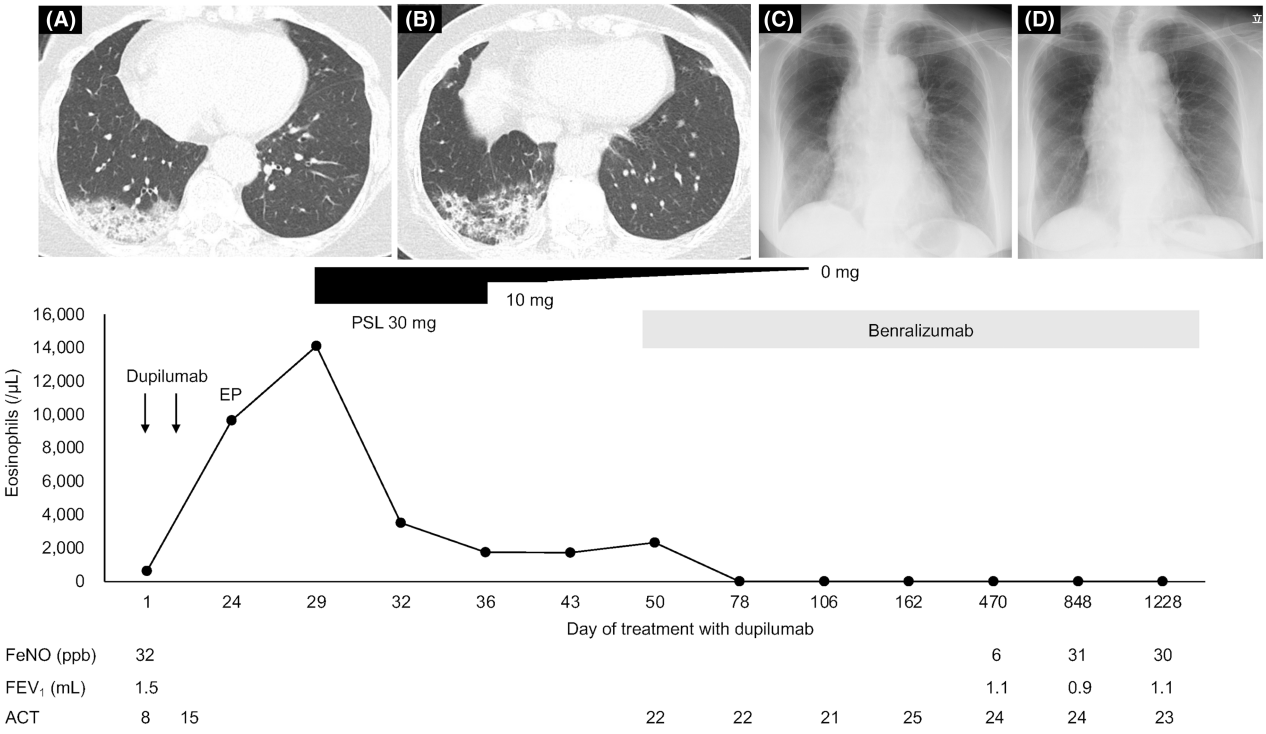

FIGURE 1 Clinical course of the patient. On Day 24 of treatment with dupilumab, the patient developed eosinophilic pneumonia (EP). On Day 29, dupilumab was discontinued and prednisolone (PSL) was started. After PSL administration, EP rapidly improved and prednisolone was tapered. On Day 50, benralizumab was started. On Day 106, PSL was discontinued. (A, B) Computed tomography (CT) of the chest at the onset of dupilumab-induced EP. On Day 24, chest CT shows nonregional consolidation, ground-glass opacity, and contractile changes in the right lower lobe. These findings are compatible with EP. (C) Chest radiography at the onset of dupilumab-induced EP. On Day 24, chest radiography shows infiltrative shadows in the right lower lung fields. (D) Chest radiography after treatment of dupilumab-induced EP. On Day 106, chest radiography shows no abnormal shadows.

included, ECRS at 42 years old. She had not been diagnosed with ABPM, AD, EGPA, or EP. Biomarkers of type 2 inflammation were as follows: IgE, 86 IU/mL (normal, < 361 IU/mL); peripheral blood eosinophils, 509/μL; and FeNO, 49 ppb. Antigen-specific serum IgE was negative. Respiratory function testing showed an FEV_1 of 2.3 L. Four months after the initial visit, the patient developed EP. Blood cell fractionation of bronchoalveolar lavage fluid at the onset of EP showed: neutrophils, 0%; eosinophils, 39%; lymphocytes, 12%; basophils, 0%; monocytes, 0%; and macrophages, 49%. She had been treated with corticosteroids for 5 months for EP. Twenty-six months after the initial visit, she lost her sense of smell. Transnasal endoscopy showed a polyp filling in the nasal cavity. Symptoms were thought to be associated with exacerbation of ECRS. The patient was treated with prednisolone, resulting in symptom improvement. However, symptoms worsened again when she discontinued prednisolone. Thirty-six months after the initial visit, subcutaneous dupilumab started being administered every 2 weeks. Symptoms gradually improved after starting dupilumab treatment. However, blood tests showed a high peripheral blood eosinophil count (Figure 2), peaking on Day 92 of dupilumab treatment at 7584/μL. On Day 158, the patient developed dyspnea. CT of the chest showed shadows consistent with recurrent EP (Figure 2A,B). As dupilumab had been successful for treating ECRS, treatment was continued and only bursts of prednisolone were administered. After starting treatment with prednisolone, EP rapidly improved. No recurrence of EP had been identified as of 10 months after discontinuing prednisolone (Figure 2C).

Case 3

A 58-year-old woman experienced repeated CEP exacerbations (Figure 3). She had first developed EP at 51 years old. No contributory medical history was elicited, including asthma, AD, or ECRS. After close examination, the EP was considered idiopathic with no involvement of drugs or EGPA. At the onset of EP, peripheral blood eosinophil count increased to 2420/μL. Blood cell fractionation of bronchoalveolar lavage fluid showed: neutrophils, 7%; eosinophils, 74%; lymphocytes, 9%; basophils, 0%; monocytes, 0%; and macrophages, 10%. Nineteen months after initial EP onset, the patient developed ECRS. Lund-Mackay score was 21. Twenty-two months after initial EP onset, the patient underwent endoscopic sinus surgery. Twenty-six months after initial EP onset, the patient experienced difficulty reducing the PSL dose due to repeated exacerbations of EP and new onset of asthma and eosinophilic otitis media. During the same period, she also reported a decreased sense of smell associated with ECRS. At

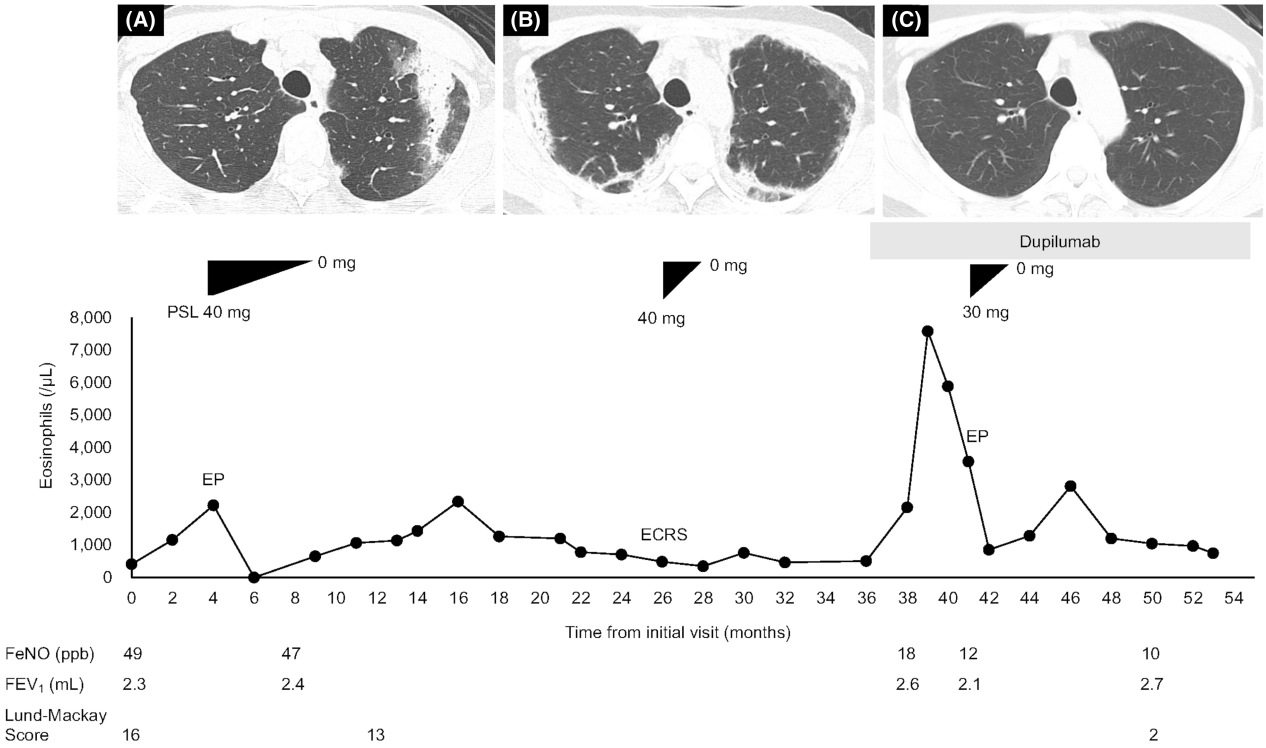

FIGURE 2 Clinical course of the patient. On Day 158 of treatment with dupilumab, i.e., 41 months after the initial visit, the patient developed eosinophilic pneumonia (EP). As treatment of eosinophilic chronic rhinosinusitis had been successful, administration of dupilumab was continued and prednisolone (PSL) was started. After PSL administration, EP rapidly improved and PSL was tapered. No recurrence of EP was seen after that. (A) Computed tomography (CT) of the chest at the onset of EP. Four months after the initial visit, chest CT shows consolidation with ground-glass opacity (GGO) in the left upper lobe. (B) CT of chest findings at the recurrence of EP. On Day 158 of treatment with dupilumab, i.e., 41 months after the initial visit, chest CT shows subpleural-predominant consolidation and GGO in bilateral upper lobes. These findings are compatible with EP. (C) CT of chest findings after treatment of recurrent EP. Fifty-three months after the initial visit, chest CT shows no abnormal shadows.

74 months after initial EP onset, subcutaneous dupilumab was administered every 2 weeks as an alternative to PSL. After starting dupilumab, PSL was discontinued and no worsening of either ECRS or EP had been seen as of 13 months after treatment with dupilumab. Further, asthma symptoms were well controlled and FEV_1 improved on respiratory function testing.

DISCUSSION

Several reports have found that dupilumab can cause EP, while others have described EP treated with dupilumab.[2–11] The mechanisms underlying dupilumab-induced EP remain unclear. However, previous reports of EP after dupilumab treatment suggest an association with hypereosinophilia. Transient hypereosinophilia is well known to occur after dupilumab administration for type 2 inflammatory disease. In randomized clinical trials, the rate of increase in peripheral blood eosinophil counts to above 3000/μL after dupilumab administration has been reported as 4%–14%.[13] The most accepted hypothesis for the mechanism of increase in blood eosinophil counts associated with administration of dupilumab is that dupilumab inhibits eosinophil migration into tissues by blocking IL-4 and IL-13-mediated production of eotaxin and vascular adhesion molecule-1, but not eosinophil production or eosinophil clearance from bone marrow.[14] On the other hand, chemokines such as CC chemokine receptor (CCR)3/CCR5 ligands, cytokines such as IL-5, lipid mediators such as leukotriene B4, damage-associated molecular pattern molecules, and extracellular matrix proteins may be involved in the accumulation and activation of eosinophils in EP.[12] Among these, IL-5 contributes to eosinophil accumulation by priming and facilitating the survival of eosinophils. According to Nishiyama et al., levels of IL-5 markedly increased in two patients who developed dupilumab-induced EP compared to patients without EP.[7] Therefore, in the pathogenesis of cases that developed eosinophilic pneumonia after treatment with dupilumab, accumulation of eosinophils by IL-5 may have been more dominant than the inhibition of eosinophil migration by blocking IL-4 and IL-13. Treatment with a biologic inhibiting IL-5 or IL-5Rα is therefore rational in cases of new-onset dupilumab-induced EP after treatment with dupilumab, as in Case 1.[15,16] However, only Kurihara et al. have described switching from dupilumab to other biologics (Table 1).[6] In contrast, Zhou et al. reported that a patient with atopic dermatitis developed dupilumab-induced EP.[3] In that case, dupilumab-induced EP improved with the administration of prednisolone and the patient was restarted

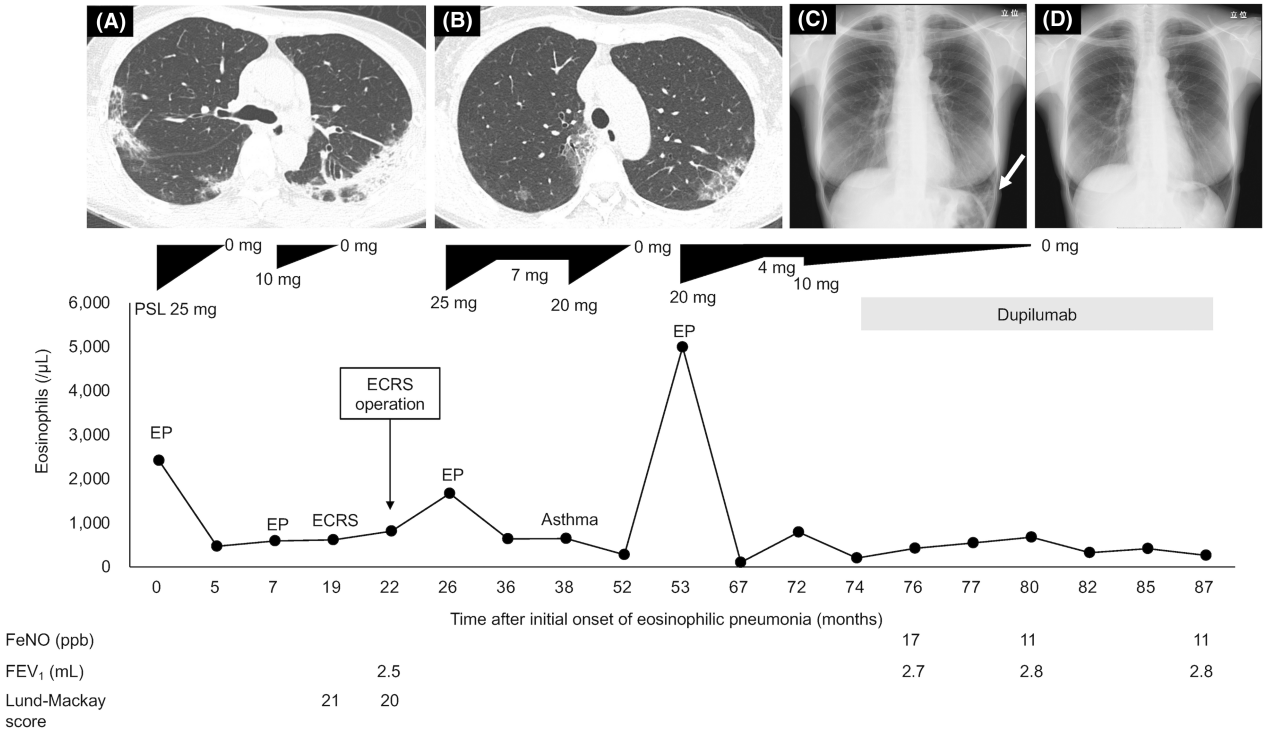

FIGURE 3 Clinical course of the patient. The patient had experienced repeated relapses of eosinophilic pneumonia (EP) after dose reductions and discontinuations of prednisolone. Dupilumab was started 74 months after first onset of EP. No recurrence of EP was seen after treatment with dupilumab. (A) Computed tomography (CT) of the chest is seen at the onset of EP. Chest CT shows subpleural and upper lobe-predominant non-regional consolidation, ground-glass opacity, and contractile changes in bilateral upper lobes. (B) Chest CT at second recurrence of EP. Twenty-six months after the initial visit, chest CT shows subpleural and upper lobe-predominant non-regional consolidation and ground-glass opacity in bilateral upper lobes. (C) Chest radiography is seen at the third recurrence of EP. Fifty-three months after the initial visit, chest radiography shows infiltrative shadows in the left lower lung fields (arrow). (D) Chest radiography after treatment with dupilumab. Eighty-seven months after the initial visit, chest radiography shows no abnormal shadows.

on dupilumab. Sudo et al. reported a patient with ECRS who developed dupilumab-induced EP.[8] In that case, dupilumab was resumed in combination with PSL after the treatment of EP.

A few case reports have also described dupilumab for type 2 inflammatory disease in patients with a history of idiopathic EP, and whether dupilumab should be continued in patients who develop exacerbation of pre-existing EP during dupilumab treatment remains unknown. Nakashima et al. reported a relapse of EP in an asthmatic patient with a history of EP, ERCS, and eosinophilic otitis media after a change from benralizumab to dupilumab.[2] In our Case 2, the patient developed a transient exacerbation of pre-existing EP after treatment with dupilumab. However, after treatment with a short burst of corticosteroids, the patient improved and was able to continue dupilumab without further flare-ups. In Case 3, the patient was treated with prednisolone and started on dupilumab for CEP and ECRS. After starting dupilumab, no exacerbation of CEP was seen and prednisolone was able to be discontinued. The hypothesis behind continuing dupilumab in Cases 2 and 3 was that IL-5 may have been less involved in cases with a history of idiopathic EP than in those with new-onset dupilumab-induced EP. In particular, the involvement of IL-4 and IL-13 may have been predominant over that of IL-5 in Case 3, in which dupilumab was successful in treating eosinophilic pneumonia. However, no studies have proven this hypothesis and further investigation is required.

In clinical trials, the safety of dupilumab was not tested in patients with eosinophil counts above 1500/μL.[14,17] Caminati et al. proposed an algorithm for the practical management of dupilumab-induced hypereosinophilia.[13] The algorithm advocates discontinuation of dupilumab in cases of organ damage associated with hypereosinophilia, although complications of idiopathic EP have not been explicitly mentioned. However, we think that treatment with dupilumab in patients with type 2 inflammatory disease and idiopathic EP is worth considering if the benefits outweigh the risks, as long as careful attention is given to the clinical course.

Limitations exist regarding the ability to interpret the findings in this case report. Not all patients with hypereosinophilia after treatment with dupilumab develop EP. However, in Cases 1 and 2, the patients developed hypereosinophilia and EP after treatment with dupilumab. Neither patient had any history of EGPA, but a small possibility remains that symptoms were masked by the use of corticosteroids, in which case the diagnosis of EGPA would not have been made correctly.

AUTHOR CONTRIBUTIONS

MH wrote the manuscript. AT, FT, and TI contributed to data collection. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

None declared.

DATA AVAILABILITY STATEMENT

Research data are not shared.

ETHICS STATEMENT

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

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