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Combination Biologic Therapy with Mepolizumab and Dupilumab for Severe Eosinophilic Granulomatosis with Polyangiitis and Chronic Rhinosinusitis with Nasal Polyp

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ABSTRACT

We report the case of a 55-year-old female with eosinophilic granulomatosis with polyangiitis and chronic rhinosinusitis with nasal polyp. Rhinosinusitis recurred 6 months after full-house endoscopic sinus surgery. Although conventional treatment with azathioprine and mepolizumab with steroids was given, it was difficult to simultaneously control both rhinosinusitis and eosinophilic granulomatosis with polyangiitis. Clinical examinations showed polyps in the olfactory cleft, and the patient's anosmia gradually became persistent. Even after administering mepolizumab for a certain period of time, symptoms did not improve, but when the biologic agent was switched to dupilumab, an improvement in recalcitrant chronic rhinosinusitis with nasal polyp was observed. While dupilumab was administered intermittently for refractory chronic rhinosinusitis with nasal polyp, the rhinosinusitis improved and symptoms such as worsening of eosinophilic granulomatosis with polyangiitis paresthesia were observed. Both symptoms gradually subsided 19 months after starting intermittent administration, leading to the discontinuation of dupilumab administration. Rhinosinusitis in the setting of eosinophilic granulomatosis with polyangiitis may be refractory in some cases, and this case provides findings demonstrating the strong effect of dupilumab on eosinophilic inflammation.

Key words asthma; biologic therapy; combination therapy; eosinophilic granulomatosis with polyangiitis; rhinosinusitis

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Abbreviations: CRSwNP, chronic rhinosinusitis with nasal polyp; ECRS, eosinophilic chronic rhinosinusitis; EGPA, eosinophilic granulomatosis with polyangiitis; FeNO, fractional exhaled nitric oxide; MPO-ANCA, myeloperoxidase anti-neutrophil cytoplasmic antibody

Eosinophilic granulomatosis with polyangiitis (EGPA) is a rare autoimmune vasculitis.[1] EGPA involves multiple organs, including the pulmonary, renal, nervous, and vascular systems.[2] The nasal cavity, including the paranasal sinuses, is one of the most frequently affected regions, along with the lower respiratory tract. Although often associated with sinusitis characterized by eosinophilic inflammation, EGPA is a completely separate disease from eosinophilic chronic rhinosinusitis (ECRS), which is potentially fatal and requires prompt systemic therapy.

The Five-Factor Score (FFS) includes cardiac, gastrointestinal, and renal disorders that when present, indicate a worse prognosis in EGPA.[3] In fact, it was reported that among patients with EGPA who were not adequately diagnosed or treated, 12% died within 1 year.[4] EGPA is usually associated with respiratory problems such as asthma, rhinosinusitis, eosinophilia, neuropathy, and vasculitis, and can also cause myocarditis and glomerulonephritis. Mepolizumab is currently recommended for this condition, in addition to the systemic use of immunosuppressants and glucocorticoids despite their inevitable side effects.[5, 6]

Most patients with EGPA have rhinosinusitis,[7] although there is only one report on the management of rhinosinusitis associated with EGPA.[8] We report the case of a patient with EGPA and refractory chronic rhinosinusitis with nasal polyp (CRSwNP) that were resistant to systemic steroids and immunosuppressants. We also successfully controlled EGPA-associated rhinosinusitis by combining mepolizumab and dupilumab.

PATIENT REPORT

We describe the case of a 55-year-old Japanese woman, a never-smoker who had required emergency hospitalization for asthma and EGPA at age 50. She was not aspirin intolerant. Prior to her hospitalization, she suddenly developed a persistent fever of 38.0°C and a cough. She refused to see a doctor for 2 weeks, and developed dyspnea, general malaise, and numbness in both lower extremities. Initial laboratory tests revealed

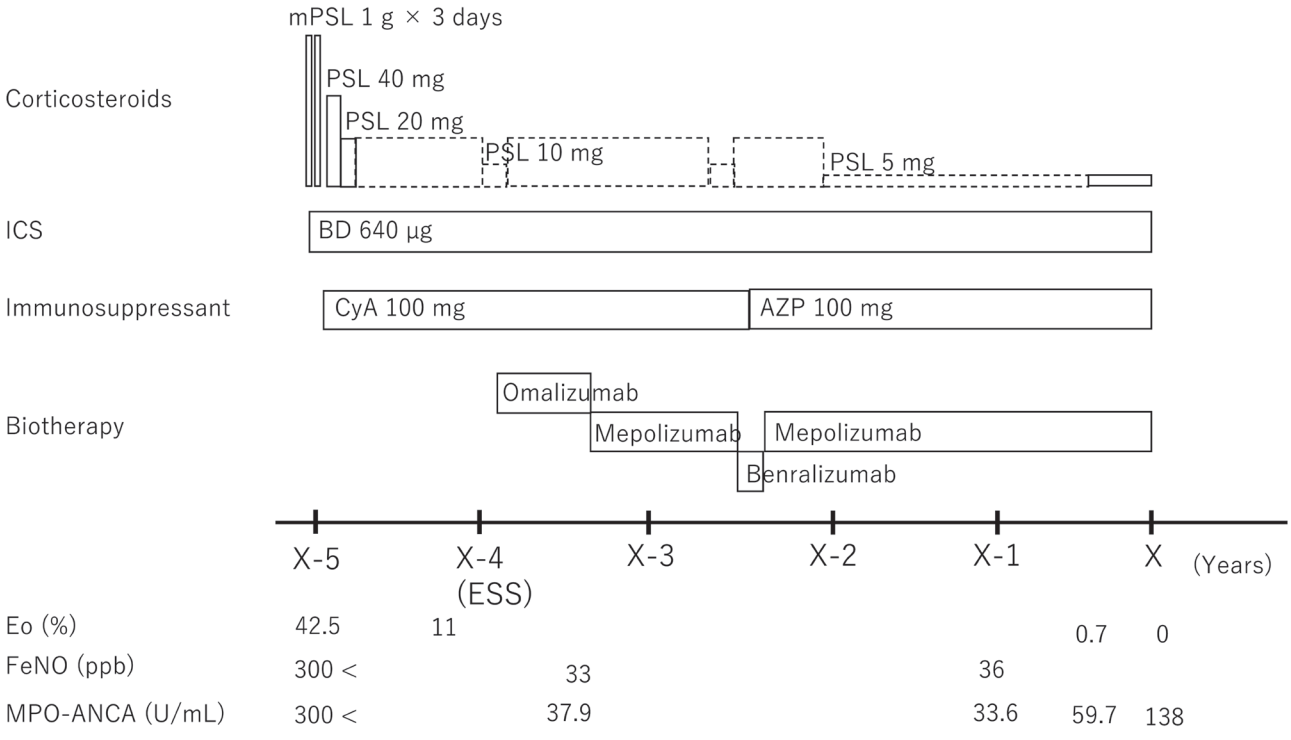

Fig. 1. Clinical course of the patient from diagnosis to readmission to our hospital. AZP, azathioprine; BD, budesonide; CyA, cyclosporine A; ESS, endoscopic sinus surgery; Eo, eosinophil; FeNO, fractional exhaled nitric oxide; ICS, inhaled corticosteroid; MPO-ANCA, myeloperoxidase anti-neutrophil cytoplasmic antibody; mPSL, methylprednisolone. Dotted squares indicate alternate daily doses. X indicates the day of reintroduction to our facility after surgery.

leukocytosis (14,600/μL, of which 42.5% were eosinophils) and a positive myeloperoxidase anti-neutrophil cytoplasmic antibody (MPO-ANCA) test (≥ 300 U/mL, normal: 3.5 ≤ IU/mL), and her fractional exhaled nitric oxide (FeNO) level was over 300 ppb. Chest computed tomography (CT) showed no abnormalities in the lung field. The patient was diagnosed with EGPA by the algorithm for classification.[9]

She had nasal obstruction and an impaired sense of smell during treatment for asthma and EGPA, and was diagnosed with chronic rhinosinusitis with nasal polyps. She was referred to our hospital and underwent full-house endoscopic sinus surgery at the age 51. The Japanese Epidemiological Survey of Refractory Eosinophilic Chronic Rhinosinusitis scoring system[10] revealed that she had a score of 17, and she was therefore diagnosed with severe ECRS. Recurrence of olfactory disturbance and postnasal drip were noted 6 months after the operation during a follow-up visit with a nearby doctor, and nasal polyps were observed. The patient complained of olfactory disturbance in particular, and conservative treatment was continued, but only temporary improvement was achieved by increasing the dose of steroids. While the respiratory medicine department was able to control the patients' EGPA and asthma (Fig. 1), re-elevated MPO-ANCA levels and continued sinusitis became an issue, and was reintroduced after surgery.

The patient was receiving prednisone 5 mg/day and azathioprine 100 mg/day, as well as mepolizumab 300 mg every 4 weeks, two puffs of budesonide 160 μg / formoterol 4.5 μg twice daily, two puffs of fluticasone furoate 55 μg once daily, and nasal irrigation with saline in both nasal cavities. Her body mass index was 20.3 kg/m^2. Her blood eosinophil fraction was 0%, and her FeNO level was 36 ppb. Her total IgE level was 11 IU/μL, whereas specific IgE levels for *Japanese cedar*, *Dermatophagoides farinae*, orchard grass, and mugwort were positive. Her serum cortisol level was 3.49 μg/dL. She complained of loss of smell. Sinus computed tomography showed significant opacity in the ethmoid sinus (Figs. 2A and B), and endoscopy showed nasal polyps in both olfactory clefts. Nasal polyps score was 6 points, using endoscopic staging method.[11] T&T olfactometry showed anosmia.

Five years after diagnosis, with the goal of strengthening the treatment of rhinosinusitis, we changed her treatment from mepolizumab 300 mg/

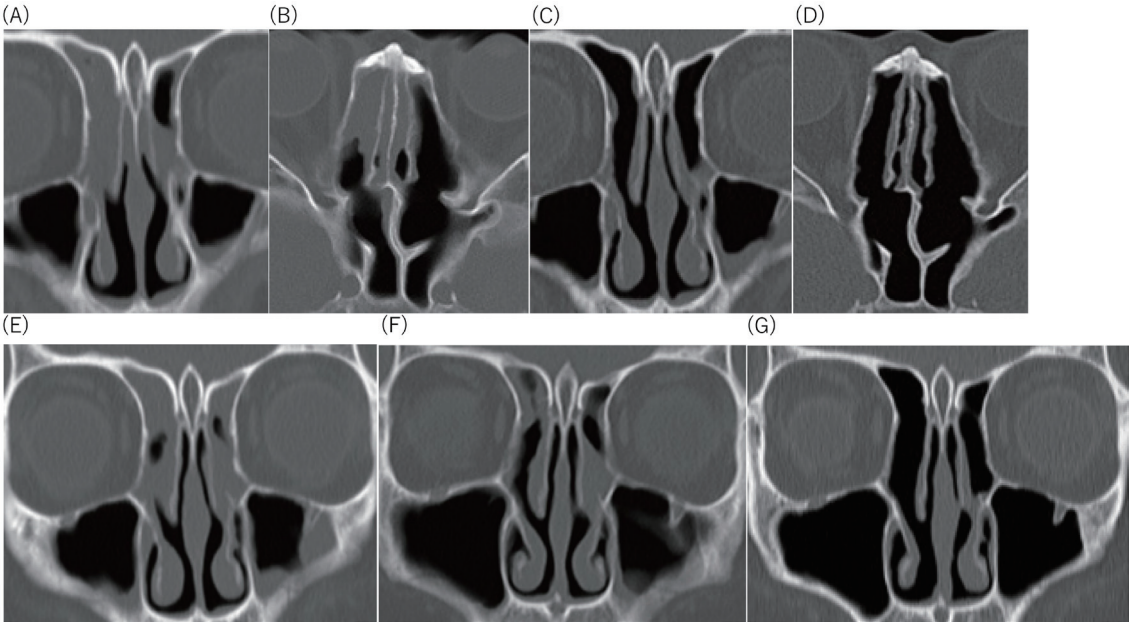

Fig. 2. Changes in CT imaging findings during biologic therapy. Coronal (**A**) and axial (**B**) CT images before dupilumab initiation; coronal (**C**) and axial (**D**) CT images after 2 doses of 300 mg dupilumab; coronal CT image after 2 cycles of mepolizumab and dupilumab (**E**); coronal CT image 13 months after starting treatment (four cycles of the combination therapy) (**F**); and coronal CT image 19 months after starting treatment (6 cycles of the combination therapy) (**G**).

month to dupilumab 300 mg every 2 weeks while taking steroids. Not only did she have no asthma attacks immediately after switching to dupilumab, but her sinus symptoms (Figs. 2C and D), including anosmia, also improved. However, the numbness due to neuropathy caused by EGPA in both extremities recurred within 2 months after starting dupilumab administration and discontinuing mepolizumab. We therefore switched her treatment back to mepolizumab and her numbness decreased 2 months later, although her rhinosinusitis worsened both symptomatically and on CT imaging (Fig. 2E). Dupilumab had to be reintroduced to relieve rhinosinusitis symptoms while mepolizumab was used to treat EGPA. Both biologics were administered intermittently while monitoring their effects and safety to avoid concurrent use (Fig. 3). Sinus CT findings were improved at 13 and 19 months after combination therapy with dupilumab and mepolizumab (Figs. 2F and G). Her daily prednisolone dose could be maintained at 5 mg. Her eosinophil fraction remained suppressed and MPO-ANCA levels decreased and no other adverse effects were observed after the start of the combination therapy. At 19 months, nasal polyps had disappeared, and dupilumab was no longer indicated for rhinosinusitis, so we decided to focus on treating EGPA with mepolizumab. Two years after starting the combination treatment, both symptoms of EGPA and rhinosinusitis have been under control.

DISCUSSION

The most frequent clinical manifestation of EGPA is respiratory tract involvement. However, patients with EGPA also often suffer from intractable rhinosinusitis,[7, 12] and these individuals have a high incidence of nasal polyps. Corticosteroids are usually sufficient for treating most patients without a poor prognostic score (FFS = 0).[3] Our patient had persistent anosmia, nasal obstruction, and rhinorrhea even after adequate medical treatment, including prednisolone, azathioprine, and biologics in addition to surgery for rhinosinusitis. Concerned about the possibility of side effects due to increased doses of steroids, we focused on the effects of EGPA and CRSwNP on eosinophilic inflammation,[13] and attempted to relieve her symptoms with systemic biologics. Depending on the clinical course and the case, the introduction of intravenous immunoglobulin may have been considered for treatment-resistant peripheral neuropathy.[13, 14]

A randomized controlled trial reported the efficacy of mepolizumab as maintenance therapy for EGPA,[6] and a case report showed the efficacy of using this agent as induction therapy.[15] Mepolizumab is an interleukin (IL)-5 inhibitor that was approved in Japan for the treatment of EGPA in 2018. IL-5 is essential for the

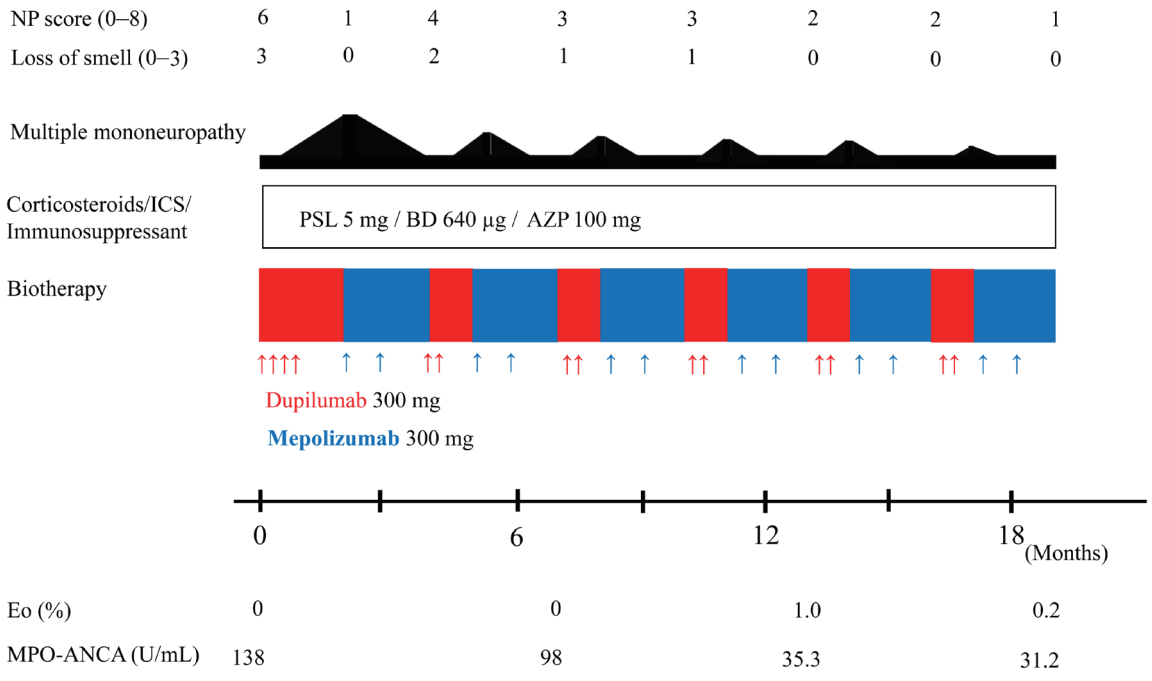

Fig. 3. Clinical course of the patient after combination therapy with dupilumab and mepolizumab. NP score indicates the sum of the nasal polyp scores for both nasal cavities using endoscopic staging method.

maturation, differentiation, and recruitment of eosinophils, and is involved in modulating their activity in allergic inflammation.[16] In this case of EGPA complicated by CRSwNP, the effect of mepolizumab monotherapy was not satisfactory.

The pathogenesis of EGPA has two components: eosinophilic inflammation and ANCA-associated vasculitis. ANCA-positive patients exhibit severe angiitis, while ANCA-negative patients show more aggressive eosinophilic infiltration.[17] The relationship between eosinophilic inflammation and ANCA titers remains unclear. In many cases of ANCA-negative EGPA, eosinophilic infiltration seems to be the main etiology because most of those cases are responsive to steroids.[1] As mentioned above, IL-5 plays a key role in eosinophilic inflammation. In individuals with ANCA-positive EGPA, such as the patient in this report, the IL-5 inhibitor mepolizumab may have an insufficient effect on EGPA complicated by eosinophilic inflammation.

Our patient, who had EGPA complicated with CRSwNP, was treated with steroids,[18] azathioprine,[18] and biologics, but rhinosinusitis symptoms only improved after we switched her from mepolizumab to dupilumab. In EGPA, increased counts of group 2 innate lymphoid cells in the peripheral blood were shown to correlate with disease activity,[19] and dupilumab suppresses the type 2 inflammation associated with these cells.[20] Mepolizumab is an anti-IL-5; its dose for EGPA is 300 mg every 4 weeks, while the same biologic product for recalcitrant CRSwNP is 100 mg ever 4 weeks. It appears that mepolizumab did not bring the benefit even using a higher dose than standard treatment for her rhinosinusitis. Dupilumab is an inhibitor of IL-4/IL-13 signaling, and it ranks among the most beneficial monoclonal antibodies in treating CRSwNP.[21] In an asthma study, switching to dupilumab significantly reduced exacerbations and maintained steroid levels in 60% of patients.[22] We found that dupilumab has the potential to provide benefit to patients like us.

New asthma treatment options involving simultaneous or alternating biologics have been reported, but these approaches have not yet been standardized (Table 1).[23–25] Although no problems have been pointed out regarding the safety of these treatments, dual therapy is expensive and is not recommended.[23, 24] With regard to severe asthma and concomitant ECRS, only one report has described the use of biologic cycling therapy with benralizumab and dupilumab.[23] In that case, the severity of the rhinosinusitis was considered to be mild because biological agent was introduced for asthma rather than CRSwNP. For asthma, treatment that includes switching between biologics be important.[26] There have been no previous reports on treating EGPA with the biologic administration method described in this case. There is still not enough consensus on using cycling biologic treatment, and this case was a special case of

Table 1. Examples of treatment options for intractable diseases

Age	Sex	Disease	Complications	Biologics	Duration of administration of biologics	Author	Year
Dual biologic therapy							
61	F	Asthma	AR CRS	Omalizumab/Dupilumab	< 12 m	Ortega et al.	2019
60	F	Asthma	AR CRS with NP	Omalizumab/Mepolizumab & Omalizumab/Benralizumab	9 m & 12 m	Ortega et al.	2019
43	M	Asthma	CRS	Omalizumab/Mepolizumab & Omalizumab/Benralizumab	24 m & < 12 m	Ortega et al.	2019
47	M	Asthma	ECRS	Omalizumab/Mepolizumab & Omalizumab/Benralizumab	6 m & 9 m	Hamada et al.	2022
Cycling biologic therapy							
43	F	Asthma	ECRS EOM	Benralizumab/Dupilumab	11 m	Hamada et al.	2021
47	M	Asthma	ECRS	Mepolizumab/Dupilumab	12 m	Hamada et al.	2022
Combination biologic therapy							
55	F	Asthma EGPA	AR ECRS	Mepolizumab/Dupilumab	19 m	Nakamura et al.	2024

AR, allergic rhinitis; CRS, chronic rhinosinusitis; ECRS, eosinophilic chronic rhinosinusitis; EOM, eosinophilic otitis media; EGPA, eosinophilic granulomatosis with polyangiitis; F, female; M, male; NP, nasal polyp.

refractory EGPA combined with CRSwNP, so we ended up using short-term combination therapy. In one study, it was reported that due to the association with anti-drug antibodies, dupilumab is therapeutically effective when administered for 8 weeks, but the therapeutic effect is lower than when it is administered for 2 or 4 weeks.[27] Previous reports on cycling therapy included switching between dupilumab and mepolizumab every month, and alternating between 2 months of dupilumab and 1 month of benralizumab.[23, 24] Therefore, from a long-term perspective, it is necessary to be careful about the dosing interval.

In conclusion, this is a unique case of EGPA with predominant eosinophilic inflammation, which was ANCA positive and complicated by CRSwNP. Furthermore, this case provides details and favorable treatment outcomes leading to alternating administration of two biologics, mepolizumab and dupilumab, for the treatment of two pathological conditions: EGPA and CRSwNP.

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The authors declare no conflicts of interest.

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