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【 CASE REPORT 】

Solo Addition of Mepolizumab Turned Antineutrophil Cytoplasmic Antibody Negative and Achieved Glucocorticoid Discontinuation in a Patient with Eosinophilic Granulomatosis with Polyangiitis

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Abstract:
The interleukin (IL)-5 inhibitor mepolizumab is beneficial in eosinophilic granulomatosis with polyangiitis (EGPA), and the inhibition of antineutrophil cytoplasmic antibody (ANCA) production has been suggested as a possible mechanism. We herein report a 78-year-old Japanese man with EGPA who received solo mepolizumab 300 mg twice for elevated ANCA levels, which led to subsequent glucocorticoid (GC) discontinuation after achieving remission. The patient was able to be freed from the adverse events associated with long-term GC treatment, and the sole addition of mepolizumab also proved that mildly elevated ANCA could be converted to a negative result, thus leading to GC discontinuation.

Key words: eosinophilic granulomatosis with polyangiitis, mepolizumab, glucocorticoid, antineutrophil cytoplasmic antibody, case report

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Introduction

Eosinophilic granulomatosis with polyangiitis (EGPA) is defined as eosinophil-rich necrotizing granulomatous inflammation, often associated with airway involvement and small- to medium-sized vasculitis (1). Eosinophils, T and B cells, neutrophils, complement system, and humoral factors are also thought to be involved in the pathogenesis but are not fully understood (2, 3).

EGPA is classified as antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis. ANCA-positive cases are characterized by renal and neurologic involvement, high C-reactive protein (CRP) levels, a fever, and myalgia; however, only 30%-40% of all patients are ANCA-positive (4, 5). The mechanism underlying ANCA production has been speculated to be the stimulation of B lymphocytes by the activation of eosinophils; however, its role in the pathogenesis of EGPA is not yet clearly understood.

Treatment strategies for EGPA consist of remission induction and maintenance therapy with glucocorticoid (GC) alone or in combination with immunosuppressants (5-7). Recently, mepolizumab, a monoclonal antibody against interleukin (IL)-5, has been recommended for both mild and refractory cases of EGPA because of its high remission induction rate, low relapse rates, and significant GC reduction compared to placebo (8). However, its efficacy in ANCA-positive cases and its effect on ANCA production has not been fully confirmed.

It has been reported that 35% of patients with EGPA experience relapse (9). In particular, given that ANCA-positive patients often relapse or are refractory to therapy, requiring long-term administration of GC and immunosuppressants and thereby leading to a poor prognosis (10), appropriate timing of mepolizumab administration is crucial in the EGPA treatment strategy.

We herein report a case of ANCA-positive EGPA with repeated relapses and GC-related adverse events during long-term maintenance therapy. Two additional doses of mepolizumab for GC monotherapy were successful in converting

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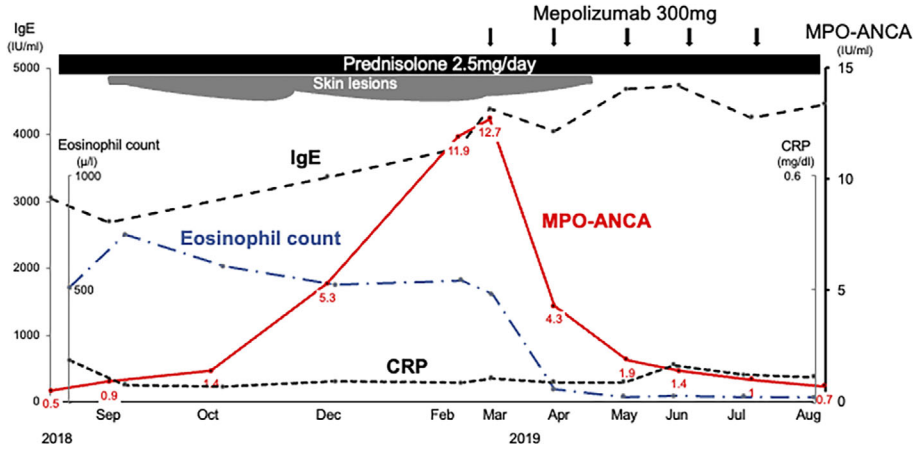

Figure 1. **Clinical course before and after initiation of mepolizumab. ANCA: antineutrophil cytoplasmic antibody, MPO: myeloperoxidase, CRP: C-reactive protein**

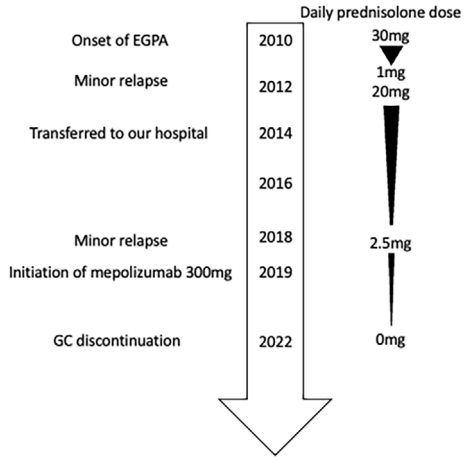

Figure 2. **Timeline from the onset of EGPA to GC discontinuation. EGPA: eosinophilic granulomatosis with polyangiitis, GC: glucocorticoid**

ANCA to a negative result, leading to the induction of remission and subsequent discontinuation of GC.

Case Report

The patient was a 78-year-old Japanese man. He developed a fever, myalgia, and cutaneous lesions at 65 years old in 2010, which had been confirmed by a skin biopsy as ANCA-positive EGPA. Only 1 score in the Five-Factor Score evaluating the prognosis at the time of diagnosis of systemic necrotizing vasculitis, namely an age >65years, was applicable. The white blood cell count was 16410/μL, with an absolute eosinophil count of 7,056/μL, myeloperoxidase (MPO)-ANCA level of 810 IU/mL (reference range, < 3.5 U/mL), and IgE level of 2,260 IU/mL (reference range, <170 IU/mL) at the onset. The patient responded to induction remission therapy with GC monotherapy equivalent to 0.6 mg/kg (30 mg/day) of prednisolone. Two years later, in 2012, the GC dose was increased again to 20 mg/day because the patient developed a minor relapse at GC 1 mg/day. Thereafter, the patient was transferred to our hospital in 2014. In 2018, at a dose of GC 2.5 mg/day, the patient experienced relapse with the development of skin lesions on the back and thighs, worsening sinusitis, and an increasing eosinophil count of approximately 500 to 1,000/μL. He also suffered visual impairment due to cataracts requiring surgery and osteoporosis as a result of long-term GC use.

Simultaneously, the MPO-ANCA levels gradually increased to 12.7 IU/mL in March 2019. The CRP level was 0.07 mg/dL, IgE level was 4,382 IU/mL, and eosinophil count was 479/μL at that time. We determined that non-GC treatment should be administered for erythema that did not respond to topical agents, which a dermatologist confirmed was due to EGPA, and for persistent nasal obstruction that impaired the quality of life. Therefore, we initiated mepolizumab at 300 mg every 4 weeks, without any increase in GC or concomitant immunosuppressants.

After 1 month, the MPO-ANCA level decreased to 4.3 IU/mL, with improvement of clinical symptoms, and became negative at 1.9 IU/mL after 2 doses. MPO-ANCA levels continued to decrease every four weeks thereafter (Fig. 1). Eosinophil counts were suppressed after four weeks of treatment with mepolizumab and remained low. Although IgE levels slowly increased during this course, there was no worsening of the clinical symptoms, such as asthma or rhinitis. Thereafter, he was able to continue mepolizumab without adverse events, and in 2022, he successfully discontinued GC after 12 years (Fig. 2).

Discussion

The rare aspect of this case is that the patient achieved ANCA negativity and GC discontinuation with only the addition of mepolizumab, without requiring an increase in GC dose or concomitant use of other immunosuppressive agents during that time.

Although MPO-ANCA levels often become negative with GC monotherapy (11), cases of decreased ANCA by mepolizumab have also been reported. One patient was treated with

a daily GC dose of 5.5 mg in combination with azathioprine, but MPO-ANCA 7 IU/mL increased to 21 IU/mL in 1 month, so mepolizumab was administered at 100 mg every 4 weeks and gradually titrated. After 5 months, the MPO-ANCA levels gradually decreased and did not deteriorate at the prescribed GC dose (12). Another patient experienced relapse after tapering the GC dose to 5 mg/day in combination with mizoribine 150 mg/day. Rhinosinusitis symptoms worsened, but there were no signs of vasculitis exacerbation, and the MPO-ANCA level was elevated at 38.7 U/mL. After 1 year of treatment with mepolizumab 300 mg every 4 weeks, the MPO-ANCA level decreased to approximately 10 U/mL (13).

There are also some reports of reduced ANCA levels with benralizumab, another IL-5 receptor antibody. In one case, the MPO-ANCA level increased to 88.0 IU/mL when GC was reduced to 6 mg/day in combination with azathioprine, without any signs of vasculitis. The symptoms improved after starting benralizumab, and MPO-ANCA decreased to 18.3 IU/mL after approximately 4 months (14). However, there is still little evidence regarding whether or not benralizumab lowers ANCA levels (15).

Eosinophils have been shown to promote the survival, activation, and proliferation of B-cells and immunoglobulin secretion by plasma cells (16). Regarding the pathogenesis of chronic rhinosinusitis, excessive production of B cell-activator factor from eosinophils may be involved via local induction of IgA and activation of eosinophils (17). However, the exact mechanism of MPO-ANCA reduction, including the effects of IL-5 inhibition on plasma cells, is not fully understood. A European multicenter study also reported negative ANCA results, although the mechanism is not clear, suggesting that the reduction in eosinophils brought about by mepolizumab may suppress B-cell activity and regulate ANCA production from plasma cells (18). Although the presence of ANCA does not always correlate with the symptoms of vasculitis (3), ANCA is known to induce vasculitis by excessive activation of neutrophils, which subsequently release inflammatory cytokines, reactive oxygen species, lytic enzymes, and excessive formation of neutrophil extracellular traps (NETs) (2). Therefore, conversion of ANCA to a negative state may significantly contribute to disease control.

In contrast, in the present case, the patient was able to discontinue GC without relapse, although there was no improvement in IgE levels after mepolizumab administration. EGPA is considered a disease in which Th2 reactivity determines the disease course, and activated Th2 lymphocytes secrete several cytokines, including IL-4, which promote eosinophil maturation in the bone marrow and activation in the periphery (19, 20). As IgE production is induced by IL-4, IgE levels are elevated in many patients with EGPA (21). Dupilumab, a fully human anti-IL-4 receptor α monoclonal antibody that blocks both IL-4 and IL-13 signaling, has been reported to be effective against relapsing or refractory sinonasal and/or asthma manifestations in EGPA, as well as against relapse in one-third of patients (22). In addition, administration of the monoclonal anti-IgE antibody omalizumab for EGPA has been reported to be ineffective and is associated with the development of EGPA (23, 24). These reports support the possibility that high IgE levels do not contribute to disease activity in EGPA and do not prevent disease remission.

In our case, GC-free remission was achieved by the addition of mepolizumab without increasing the GC dose or adding immunosuppressants. GC monotherapy remains valuable for induction of remission for patients with non-severe disease, but it has a high relapse rate (25, 26) in addition to adverse events. Furthermore, the efficacy of azathioprine used in maintenance therapy has been reported to be equivalent to that of placebo (27), suggesting a lack of evidence regarding the use of immunosuppressants in combination therapy. Rituximab is also a recommended agent that reduces IL-5 production by inhibiting crosstalk between B and T cells, as well as ANCA production from B cells (28). However, it is still difficult to completely control EGPA with a single agent because of the coexistence of two pathological conditions: eosinophilic inflammation and vasculitis.

However, there are increasing reports on the efficacy of mepolizumab in ANCA-positive cases. A recent study using data from the MIRRA study showed a clinical benefit with mepolizumab regardless of the vasculitis phenotype (29), while only about 10% of ANCA-positive cases were included in the study (7). In our recent study of 27 cases, mepolizumab treatment achieved nearly half of the GC-free remissions in a population that included 40% MPO-ANCA-positive cases (30). Mepolizumab is also effective for long-term monotherapy, as its safety profile is similar to that of a placebo (7). As in previous case reports, the signs of disease relapse in this patient were relatively minor, suggesting eosinophilic infiltration. Because of the low titer of MPO-ANCA in this patient, it is possible that the disease may have improved with mepolizumab but also could have ameliorated spontaneously. However, in the absence of a reliable index that can predict a relapse of EGPA, it has been reported to be associated with a relapse (31), and a 300 mg dose of mepolizumab is clearly more effective than a 100 mg dose in its treatment (23). Furthermore, GC escalation is inevitable upon relapse, leading to organ damage (10).

In the present case, disease relapse was prevented by administering 300 mg of mepolizumab without missing the timing of ANCA elevation; thus, routine measurement of ANCA levels may also contribute to avoiding adverse events caused by GC accumulation.

Written informed consent was obtained from the patient for the publication of this case report.

Author's disclosure of potential Conflicts of Interest (COI).
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