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Case Report

MPO-ANCA-positive eosinophilic granulomatosis with polyangiitis complicated by alveolar haemorrhage treated with mepolizumab as an induction therapy: Case report

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ABSTRACT

Eosinophilic granulomatosis with polyangiitis (EGPA) is a systemic vasculitis preceded by bronchial asthma or allergic sinusitis and accompanied by peripheral blood eosinophilia. Immunosuppressive drugs, such as cyclophosphamide in addition to high-dose glucocorticoids (GCs), are recommended for induction of remission in patients with severe EGPA. Although mepolizumab is widely recognised as remission induction therapy in nonfatal/nonorgan disabling or relapsed/refractory EGPA, its efficacy and safety in induction of remission for severe cases have been ambiguous. In this context, we report a case of myeloperoxidase antineutrophil cytoplasmic antibody-positive severe EGPA in which the patient had a favourable course using mepolizumab as an induction remission therapy. The patient, a 74-year-old man, had myeloperoxidase antineutrophil cytoplasmic antibody-positive severe EGPA with alveolar haemorrhage. High-dose GCs and intravenous cyclophosphamide were started as remission induction therapy. However, after the initiation of intravenous cyclophosphamide, alveolar haemorrhage worsened, and there was development of opportunistic infections, such as aspergillus and cytomegalovirus antigenaemia. Treatment with the antifungal drug voriconazole and the antiviral drug ganciclovir was started for opportunistic infection, and the treatment for EGPA was switched from intravenous cyclophosphamide to mepolizumab. As a result, alveolar haemorrhage improved, GCs were reduced, and the infection also improved. Mepolizumab as remission induction therapy for severe EGPA were thought to be appropriate and effective treatment in this case. However, the efficacy and safety of mepolizumab for this purpose require comprehensive evaluation.

KEYWORDS: Eosinophilic granulomatosis with polyangiitis; mepolizumab; induction therapy

Introduction

Eosinophilic granulomatosis with polyangiitis (EGPA) is a systemic inflammatory autoimmune disease that is preceded by bronchial asthma and allergic sinusitis, accompanied by peripheral blood eosinophilia and symptoms of vasculitis such as polyangiitis. The 2022 American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology (EULAR) Clinical Practice Guidelines recommend the use of intravenous cyclophosphamide (IVCY) and rituximab (RTX), a chimeric anti-CD20 antibody as B-cell-depleting therapy, as induction remission therapy for severe EGPA in addition to high-dose glucocorticoids (GCs) [1]. In Japan, however, RTX is not approved for treatment of EGPA, and the Vasculitis Group of the (Japanese) Ministry of Health, Labour and Welfare 2023 guidelines instead recommend the introduction of IVCY as an induction remission therapy for severe EGPA.

Mepolizumab was approved in Japan in 2018 for the treatment of EGPA refractory to existing therapies, such as GC. Mepolizumab is recommended in the 2021 ACR practice guidelines as a treatment for induction of remission in non-severe EGPA and maintenance of remission in severe EGPA [2]. In the treatment of severe EGPA, especially cases with potentially fatal conditions such as alveolar haemorrhage, it can be difficult to select treatment. For example, under the current Japanese guidelines, RTX cannot be used when IVCY is discontinued as a result of side effects or concomitant infections.

As an alternative, mepolizumab has been suggested as a remission induction therapy and there has been discussion of its efficacy [3]. In this context, we propose the importance of reporting the efficacy and safety of mepolizumab in serious cases (e.g. alveolar haemorrhage) and to accumulate cases.

Here, we therefore present a case of severe EGPA complicated with alveolar haemorrhage, which worsened after a single dose of IVCY with methylprednisolone (mPSL) pulse and high-dose GC. The patient also developed opportunistic

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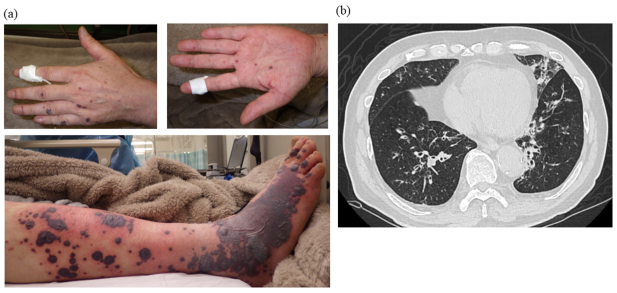

Figure 1. (a) Blood blisters in extremities. After admission, purpura appeared on the right dorsal foot, merged and expanded. Later, purpura spread to the left leg, both fingers and palms, and painful blood blisters developed. (b) CT of the chest on admission shows diffuse airway infiltration in both upper lobes of the lungs, suggesting alveolar haemorrhage.

infections, such as aspergillus and cytomegalovirus antigenaemia. After switching from IVCY to mepolizumab, the patient had a favourable course.

Case presentation

A 74-year-old man was diagnosed with bronchial asthma 9 years previously. He had anorexia for a month, and was admitted to a hospital because of no improvement. He had a fever of ≥38°C of unknown cause. Purpura appeared on the dorsum of his right foot, which fused and enlarged. The purpura further spread to the left lower extremity, both fingers, and palms, causing painful blood blisters. Blood tests showed eosinophilia and elevated C-reactive protein (CRP). EGPA was suspected, so the patient was transferred to our department. The patient had haemoptysis, bloody sputum and hypoxaemia with SpO_2 89% (room air), and purple spots and blood blisters with infiltration on the bilateral dorsal surfaces of the hands, palms, and both lower limbs (Figure 1(a)). Neurological findings were unremarkable. The main laboratory findings on admission are shown in Table 1. Urinalysis showed protein ±, occult blood reaction 2+, erythrocytes 10–19/HF, epithelial column 1–9/HF, and erythrocyte column 1–9/HF. Blood tests showed WBC 32,000/μl, eosinophils 70%, eosinophil count 22,400/μl, CRP 9.14 mg/dl, and myeloperoxidase antineutrophil cytoplasmic antibody (MPO-ANCA) 73.4 IU/ml. Chest computed tomography (CT) showed diffuse airway infiltrates in the upper lobes of both lungs (Figure 1(b)). A biopsy of the purpura on the thigh was taken and histological examination revealed infiltration of neutrophils and eosinophils in vessel walls of the dermis to the subcutaneous tissue and fibrinoid necrosis, but there was no observation of granuloma (Figure 2).

According to the 2022 ACR/EULAR EGPA classification criteria, we classified the patient as having EGPA with a total of 9 points (6 or more), including a history of bronchial asthma (+3), a eosinophil count $\geq 1 \times 10^9$ (+5), a biopsy finding of extravascular eosinophilic inflammation (+2), and haematuria (−1). According to the 1998 Ministry of Health, Labour and Welfare diagnostic criteria, he met the major clinical findings [bronchial asthma, eosinophilia, symptoms of vasculitis (fever, purpura)] and the major histological findings (fibrinoid necrotising vasculitis with marked eosinophilic infiltration of surrounding tissues) and it was suggested to be a clear case of EGPA. Critical EGPA is defined as EGPA with life- or organ-threatening symptoms and is associated with alveolar haemorrhage, glomerulonephritis, central nervous system vasculitis, polyangiitis, cardiac involvement, mesenteric ischaemia, and limb and fingertip ischaemia [1, 2]. Bronchoalveolar lavage was not performed due to the high risk of hypoxia. However, because haemoptysis and bloody sputum were observed and because CT showed diffuse airway infiltration typical of alveolar haemorrhage, we diagnosed alveolar haemorrhage and severe EGPA. Furthermore, Hb was 14.5 g/dl on Day 1, but had decreased to 9.1 g/dl on Day 16, indicating progressive anaemia. Other diseases that cause alveolar haemorrhage include systemic autoimmune diseases such as systemic lupus erythematosus and infectious diseases, and drug effects, but all of them were considered to be negative in this case based on medical history and test results.

The patient received mPSL pulse therapy for 3 days from the day of admission, followed by prednisolone (PSL) 75 mg/day (1 mg/kg/day). However, on Day 6, there was deterioration in oxygenation, going from needing a mask oxygen supply of 2 l/min to requiring a high-flow nasal cannula supplying 40 L, 50%. CT on Day 6 showed worsening pulmonary infiltrates (Figure 3(a)). The patient underwent his first IVCY on Day 7. From Day 14, he underwent plasmapheresis, but due to allergic reactions including skin rash it was discontinued after the fourth treatment. CT at that time showed further worsening pulmonary infiltrates on Day 19 (Figure 3(b)). He developed cytomegalovirus antigenaemia [cytomegalovirus-positive cell count: 18 (C7-HRP method)] on Day 13 and aspergillus infection (aspergillus antigen titer: 0.8) on Day 19. Continuing IVCY thus became difficult, so he was instead started on mepolizumab 300 mg/month. After starting mepolizumab, the oxygenation was improved, and oxygen administration was no longer required on Day 33. Blood sputum disappeared on Day 36, and blood test results improved (Figure 4). Furthermore, CT on Day 34 showed improvement in the diffuse airway infiltrates in both lobes (Figure 3(c)). The blood blisters did not spread after the start of treatment. Some were ulcerated, but then gradually improved and healed. On Day 50, the patient was transferred to another hospital for recuperation, and he was discharged home on Day 77. On Day 138, the dose of PSL was reduced to 12 mg, and his blood test improved to CRP 0.02 mg/dl and MPO-ANCA 4.7 IU/ml (Figure 4). These levels have been maintained since then. The patient has provided informed consent to publication of the details of his case and the accompanying images.

Discussion

We administered mPSL pulse therapy, high-dose GC, and IVCY in the case of a patient with severe EGPA complicated with alveolar haemorrhage. However, the alveolar haemorrhage worsened and the patient developed opportunistic infection, which may have had an effect on the alveolar haemorrhage. After switching from IVCY to mepolizumab, the patient had a favourable prognosis.

The practice guidelines for ANCA-associated vasculitis published by the ACR in 2021 define severe EGPA as that with life- or organ-threatening symptoms and complications such as alveolar haemorrhage, glomerulonephritis, central nervous

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Table 1. Laboratery data from the time of admission

Haematology		Normal range	Immunology		Normal range
White blood cells	32,000/μl	3300 ~ 8600	IgG	1602 mg/dl	861 ~ 1747
Eosinophil	70%		IgA	189 mg/dl	93 ~ 393
	22,400/μl		IgM	56 mg/dl	33 ~ 183
Red blood cells	481 $\times 10^6$/μl	435 ~ 555	IgE	3057 mg/dl	0 ~ 358
Haemoglobin	15.4 g/dl	13.7 ~ 16.8	PR3-ANCA	<0.6 IU/ml	<2.0
Platelet	23.8 $\times 10^4$/μl	15.8 ~ 34.8	MPO-ANCA	73.4 IU/ml	<3.5
Biochemistry/Serology			Rheumatoid factor	39.4 IU/ml	<15
Total protein	6.9 g/dl	6.6 ~ 8.1	Urine		
Albumin	2.7 g/dl	4.1 ~ 5.1	pH	6.5	5.0 ~ 7.5
AST	26 IU/l	13 ~ 30	Urine specific gravity	1.027	1.005 ~ 1.030
ALT	40 IU/l	7 ~ 23	Protein	(±)	(-)
LDH	359 IU/l	124 ~ 222	White blood cells	0 ~ 1/HPF	<5
BUN	15.3 mg/dl	8 ~ 20	Red blood cells	10 ~ 19/HPF	<5
Creatinine	1.15 mg/dl	0.46 ~ 0.79	Cast hyaline cylinder	1 ~ 9/WF	
Na	136 mEq/l	138 ~ 145	Epithelial cylinder	1 ~ 9/WF	
K	4.5 mEq/l	3.6 ~ 4.8	Waxy cylinder	1 ~ 9/WF	
Cl	99 mEq/l	101 ~ 108			
CRP	9.14 mg/dl	0.00 ~ 0.14			
ESR	30 mm/h	0 ~ 15			
KL-6	230 U/l	105.3 ~ 401.2			
SP-D	206.8 ng/ml	<110			

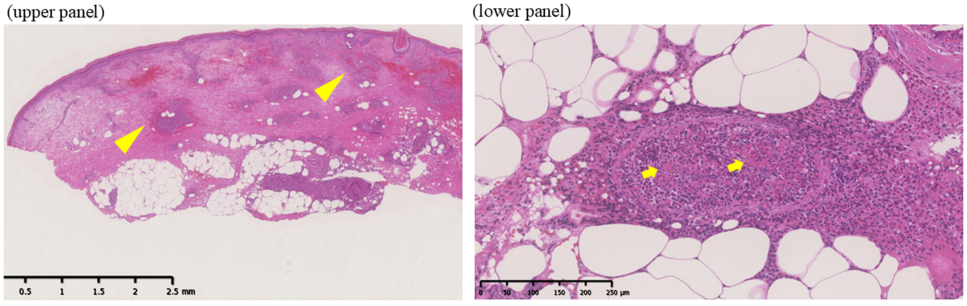

Figure 2. Pathological findings of purpura on the thighs. PAS staining (upper panel): infiltration of neutrophils and eosinophils was observed in the dermal to subcutaneous fatty tissue vessel walls, and (lower panel) fibrinoid necrosis was confirmed, but no granulomas were observed.

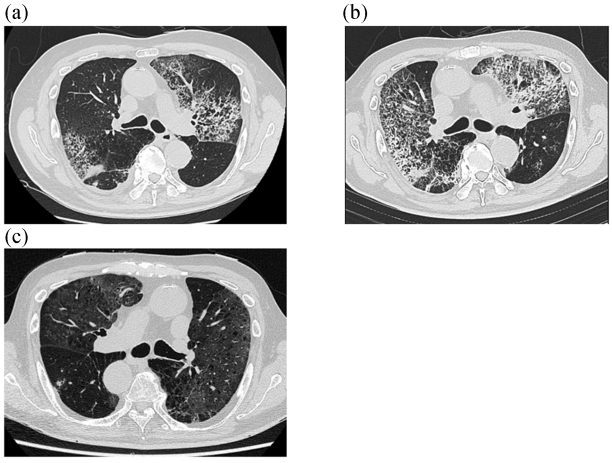

Figure 3. From left to right, CT scan of the chest on Day 6 before IVCY treatment (a), Day 19 after IVCY treatment (b), and Day 34 after mepolizumab treatment (c). There was improvement of diffuse airway infiltrates in either of the upper lobes that were present at the time of admission.

system vasculitis, cardiac involvement, mesenteric ischaemia, and limb and fingertip ischaemia. Accordingly, the present case is considered to be a severe case of EGPA [1, 2]. Different evidence-based 2023 EGPA guidelines by a core committee consisting of experts in various fields define a severe case as the presence of Five Factor Score ≥1, peripheral neuropathy, alveolar haemorrhage, or other organ- or life-threatening symptoms [4]. Our patient had alveolar haemorrhage, so met the criteria for severe EGPA under both definitions.

For remission induction therapy for severe EGPA, the 2022 EULAR treatment recommendations for ANCA-associated vasculitis recommend the use of mPSL pulse therapy, high-dose GC, IVCY, and RTX [1]. On the other hand, mepolizumab is recommended for induction of remission in nonfatal/nonorgan disabling or relapsed/refractory EGPA and maintenance of remission in severe EGPA [2, 4]. However, the efficacy and safety of mepolizumab for induction of remission in severe EGPA are unclear, and mepolizumab is not recommended in guidelines from other countries.

Mepolizumab inhibits IL-5 signalling and suppresses eosinophil proliferation by inhibiting IL-5 binding to the α chains constituting IL-5 receptors expressed on the surface of eosinophils [5]. Conversely, in MPO-ANCA-positive EGPA, neutrophils are firstly primed by inflammatory cytokine and complement substitution pathways. Secondly, ANCA binds to primed neutrophils via Fcγ receptors or MPO proteins

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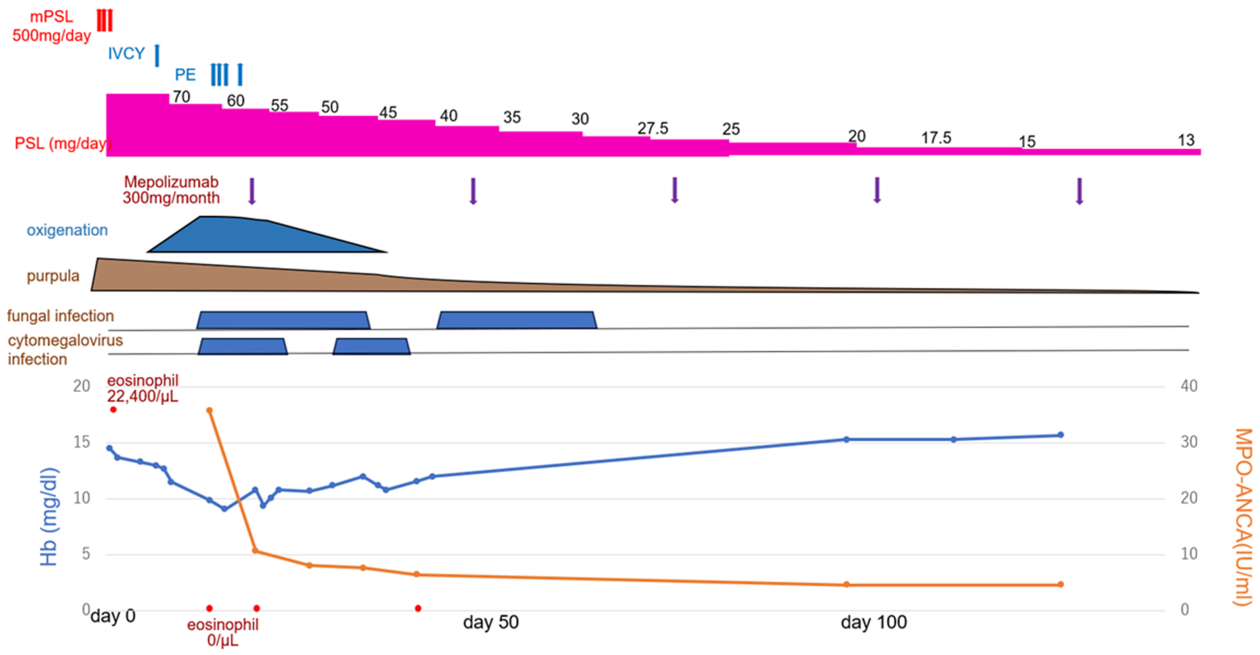

Figure 4. Clinical course. mPSL pulse therapy was administered for 3 days from the day of admission, after which oral high-dose GCs were initiated. The patient's oxygenation worsened on Day 6. IVCY was first administered on Day 7 and plasmapheresis was started on Day 14. On Day 13 and Day 19, he developed cytomegalovirus and aspergillus infections, respectively, which made it difficult to continue IVCY. Then mepolizumab 300 mg/month wasstarted, oxygenation improved, and the eosinophil count decreased to 0/μl, CRP to 0.03 mg/dl, and MPO-ANCA to 7.7 IU/ml on Day 33. On Day 138, the dose of PSL was reduced to 12 mg, and his blood test results improved to CRP 0.02 mg/dl and MPO-ANCA 4.7 IU/ml. Since then, these levels havebeen maintained.

expressed on the cell surface, resulting in the production of reactive oxygen species, the release of proteolytic enzymes, and formation of neutrophil extracellular traps. In the case of alveolar haemorrhage in EGPA, the pathology due to vasculitis is considered, and the use of RTX might be used in countries where it is approved. However, EGPA suggests that eosinophils are closely involved in the pathophysiology of both MPO-ANCA-positive and negative cases [6], and the pathophysiology of alveolar haemorrhage associated with this disease is still unclear. Mepolizumab may become an option, suggested by the favourable course of treatment with mepolizumab in this case. We would like to further discuss the mechanism of action of mepolizumab, which showed a favourable course in patients with MPO-ANCA-positive and alveolar haemorrhage.

The differences between cases of MPO-ANCA-positive ANCA-associated vasculitis and cases of MPO-ANCA-positive/negative EGPA have been investigated according to clinical features and in genome-wide association studies [7, 8]. The cases of MPO-ANCA-positive EGPA were suggested to be a typical human leucocyte antigen class II-associated autoimmune disease based on eosinophilia. Conversely, in cases of MPO-ANCA-negative EGPA, the autoantibodies are not associated with human leucocyte antigen class I or class II alleles, suggesting that there is less of an autoimmune component and a genetic association with GPA33 expression, a barrier protein, which may arise from mucosal/barrier dysfunction [6, 7]. As for the mechanism by which mepolizumab was useful in this severe case of MPO-ANCA positivity, eosinophils produce IL-4, 5, 6, etc., and are indirectly involved in the differentiation of helper T cells and B cells [9]. In other words, the regulation of eosinophils by mepolizumab may have improved alveolar haemorrhage via vasculitis control that indirectly involves lymphocyte activation and differentiation. A report that mepolizumab reduced MPO-ANCA supports this hypothesis [10]. Peripheral neuropathy in EGPA reportedly involves not only vasculitis but also obstruction by eosinophils in the capillaries [11].

Although there are no previous reports of microvascular thrombosis caused by eosinophils in alveolar haemorrhage, in this case, we could not rule out the possibility that microthrombosis caused by eosinophils was involved in the alveolar haemorrhage. There may be a possibility that cytomegalovirus or aspergillosis may have contributed to the worsening of alveolar haemorrhage at the site of pulmonary lesions, and that mepolizumab, which has a less immunosuppressive effect, may have been useful in addition to treatment against these infections.

In a previous study of mepolizumab as induction remission therapy for EGPA, patients with severe relapsed/refractory EGPA treated with high-dose steroids and mepolizumab (seven patients) were compared with those treated with high-dose steroids and cyclophosphamide (13 patients). The Birmingham Vasculitis Activity Score, Vascular Damage Index, and eosinophil counts did not differ between the two groups, but the concomitant GC dose was significantly lower in the mepolizumab group after the third month [3]. Only two patients with MPO-ANCA-positive EGPA were treated with mepolizumab. As a further limitation, the impact of the four plasmaphereses performed immediately prior to the introduction of mepolizumab was unclear. However, the improvement of symptoms such as alveolar haemorrhage after the start of mepolizumab and the subsequent favourable course over the long term were considered to be largely due to the effect of

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continuous administration of mepolizumab from the induction phase of remission. There are also previous reports of early introduction of mepolizumab in patients with MPO-ANCA-negative EGPA, which have shown efficacy [12]. However, the use of mepolizumab as remission induction therapy for MPO-ANCA-positive EGPA has not been widely reported, and further studies are required.

Conclusion

Mepolizumab was suggested to be useful in the treatment of our patient with alveolar haemorrhage associated with EGPA. RTX cannot be used in some countries for the treatment of severe EGPA if IVCY is discontinued as a result of side effects or concomitant infections, especially in potentially fatal cases such as of alveolar haemorrhage. Selection of treatment is therefore difficult. Reporting the efficacy and safety of mepolizumab in serious cases is therefore of great importance. The involvement of eosinophils in the organs of patients with serious diseases such as alveolar haemorrhage also requires elucidation.

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Conflict of interest

None declared.

Funding

None declared.

Patient consent

The patient has provided informed consent to publication of the details of his case and the accompanying images.

Ethical approval

Not applicable.

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