Renal Replacement Therapy

CASE REPORT

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Successful treatment with rituximab and plasmapheresis of renal involvement of eosinophilic granulomatosis with polyangiitis

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Abstract

Background Eosinophilic granulomatosis with polyangiitis (EGPA) is a rare disorder characterized by asthma, eosinophilia, and systemic vasculitis. Renal involvement is not regarded as a prominent feature and the treatment is still under study.

Case presentation A 68-year-old woman was admitted to our hospital because of fever, renal dysfunction, eosinophilia, and the presence of MPO-ANCA. Based on the renal pathological examination which showed extravascular eosinophilic-predominant inflammation and crescentic glomerulonephritis, EGPA was diagnosed. Considering the acute kidney injury, prominent eosinophilia, and strongly positive anti-MPO antibodies, pulse steroid therapy was administered, followed by intravenous rituximab. Plasmapheresis was also provided (9 sessions). The eosinophil count was normalized, and renal dysfunction was reversed. The patient no longer requires dialysis.

Conclusions Renal involvement of EGPA is rare, and consensus on its treatment is still lacking, because of a lack of large-scale randomized controlled trials. We treated our patient as a case with high severity. For patients with severe disease, the addition of cyclophosphamide to glucocorticoid therapy is commonly used. However, rituximab and plasmapheresis combined with systemic glucocorticoid therapy were found to be beneficial because the renal function and other clinical conditions were almost fully recovered. Thus, our treatment is highly effective against renal involvement of eosinophilic granulomatosis with polyangiitis.

Keywords Eosinophilic granulomatosis with polyangiitis, Renal involvement, Rituximab, Plasmapheresis

Background

Eosinophilic granulomatosis with polyangiitis (EGPA) is a rare and potentially fatal disease. The prevalence in Europe ranges from 10.7 to 14/million. In the USA, the prevalence is approximately 18/million. The highest prevalence reported is from Australia, at 22.3 cases/million [1]. This condition is defined by the presence of eosinophil-rich and necrotizing granulomatous inflammation. Neurological and respiratory involvement is a common feature, whereas renal involvement is extremely rare. The treatment is still under study. We successfully treated a patient admitted for renal impairment whose diagnosis was EGPA.

Case presentation

A 68-year-old Japanese woman was admitted to our medical unit because of fever, nausea, and loss of appetite. She had occasionally suffered from mild asthma. A physical examination showed livedo reticularis, particularly of her lower limbs. Chest computed tomography (CT)

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showed fatty liver. Laboratory tests revealed the presence of increased creatinine (4.33 mg/dL) and MPO-ANCA (241 U/mL) with eosinophilia (2.36×10^3 μL, 24.9%).

On the 3rd day, kidney biopsy was performed. Renal pathological examination showed extravascular eosinophilic-predominant inflammation and crescentic glomerulonephritis. As a result, EGPA was diagnosed. Therefore, intravenous glucocorticoid (methylprednisolone 500 mg daily for three days) was used as the initial therapy, followed by oral glucocorticoid therapy (30 mg per day as an initial dose), with the prompt regression of blood eosinophilia. In addition, rituximab and plasma exchange (9 sessions) were started in conjunction with systemic glucocorticoid therapy. New blood work revealed decreased creatinine (2.19 mg/dL), with a surprising decrease in MPO-ANCA (4.1 U/mL). On the other hand, high levels of proteinuria (2.58 g/gCr) were noted on urinary analysis. She was discharged after 53 days of hospitalization with persisting proteinuria. As regards her follow-up, the corticosteroid dose was gradually tapered to a maintenance dose. Two months after discharge, and no longer requires dialysis.

Discussion

EGPA, also known as Churg–Strauss Syndrome, is a small vessel ANCA-associated vasculitis typically characterized by the triad of asthma, eosinophilia, and vasculitis. The vasculitis is often not apparent in the initial phases of the disease. Extrapulmonary manifestations can include constitutional symptoms (50–90%), musculoskeletal (50%) or cutaneous disease (40–70%), and peripheral nervous system (>50%), cardiac (30 to 50%), and gastrointestinal (30–50%) involvement. Many patients with EGPA do not have glomerulonephritis [2]. The frequency of renal involvement varies among studies. In the largest series of 383 patients with EGPA, renal involvement was noted in 83 patients (22 percent) [3]. Of interest, only 25% of patients with EGPA who have no renal disease are ANCA-positive, whereas 75% with any renal disease, and 100% with documented necrotizing glomerulonephritis show ANCA-positivity [4]. Significant ANCA serum concentrations are found in approximately 40% of patients with EGPA, and most of these patients are MPO-ANCA-positive [5]. Given the high severity in this case with rapidly progressive glomerulonephritis, rituximab and plasma exchange were started with systemic glucocorticoid therapy. The response to rituximab was assessed in a retrospective study of 41 patients treated at four highly specialized vasculitis centers [6]. After the first infusion of rituximab, improvements in disease activity (remission and partial response) were achieved in 83 percent of patients at six months, and at 12 months, the improvement rate was nearly 90 percent. Rituximab may also have efficacy for active, severe disease as pointed out by 2021 American College of Rheumatology/Vasculitis Foundation Guideline. Plasma exchange has occasionally been used in conjunction with other therapies, but a meta-analysis involving 140 patients with glomerulonephritis due to EGPA or microscopic polyangiitis found that it added no benefit to treatment with glucocorticoids [7]. It is generally reserved for patients with rapidly progressive glomerulonephritis and diffuse alveolar hemorrhage [8]. Our patient's clinical condition markedly improved, especially renal involvement, after treatment with rituximab and plasma exchange.

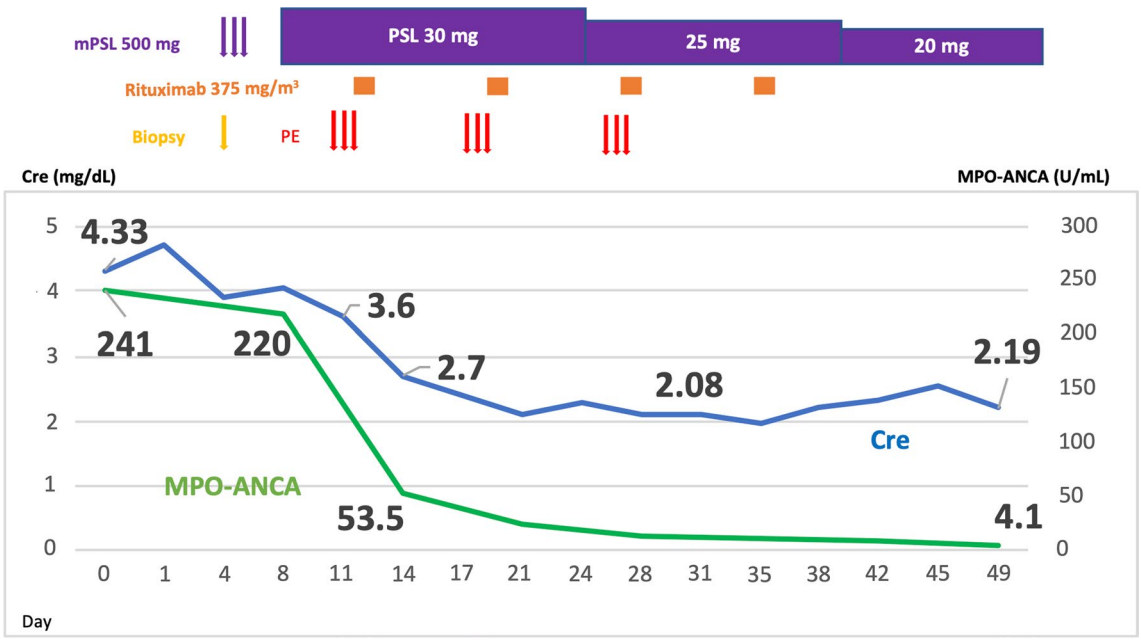

Fig. 1 Clinical course on admission

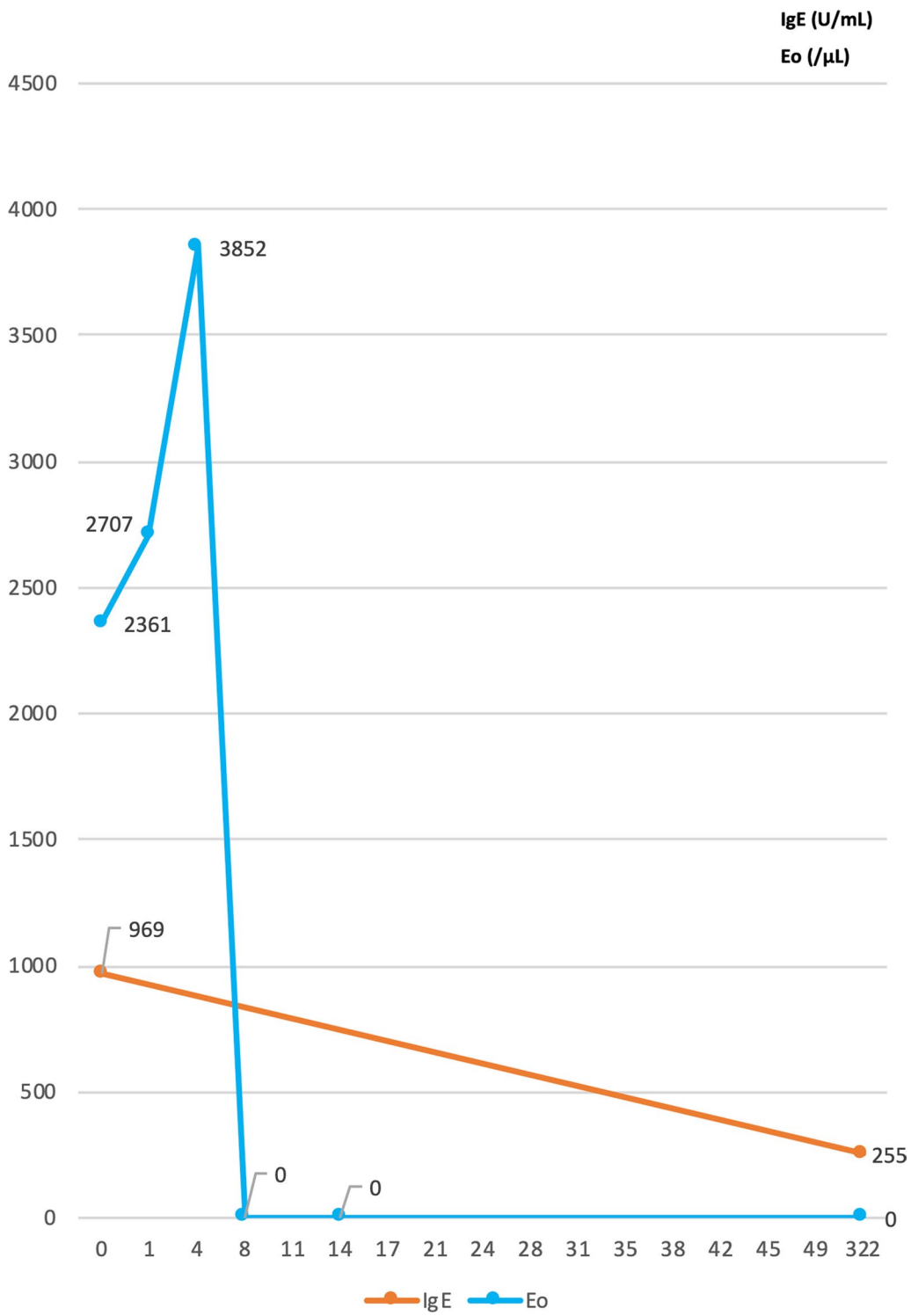

Fig. 2 Time course of IgE and eosinophils

Mini review

Patients with the renal involvement of EGPA are defined as active severe EGPA by the ACR guidelines. They suggest either IV pulse glucocorticoids (IV methylprednisolone 500–1000 mg/day) or high-dose oral glucocorticoids (prednisone 1 mg/kg/day) be prescribed as initial therapy. There are no data to support favoring either IV pulse or high-dose oral glucocorticoids

Table 1 Summary of the patient's blood and urine test results

TP	6.2	g/dL	WBC	94.8×10^2	/μL
Alb	2.8	g/dL	Neu	61	%
BUN	42	mg/dL	Lym	11	%
Cre	4.33	mg/dL	Mono	2.6	%
AST	13	IU/L	Eosin	24.9	%
ALT	11	IU/L	Baso	0.5	%
LD	186	IU/L	RBC	335×10^4	/μL
CK	37	IU/L	Hb	9.9	g/dL
TG	133	mg/dL	PLT	28×10^4	/μL
T-cho	226	mg/dL	IgG	1270	mg/dL
LDL-C	145	mg/dL	IgA	132	mg/dL
CRP	7.45	mg/dL	IgM	44	mg/dL
Na	135	mEq/L	IgE	969	IU/mL
K	3.9	mEq/L	MPO-ANCA	241	U/mL
Cl	101	mEq/L	PR3-ANCA	< 1.0	U/mL
pH			5.5		
Urine protein			3+		
Urine occult blood			3+		
RBC			25		/HPF
U-TP/U-Cr			2.19		g/gCr

over the other option in active, severe EGPA. Choosing an approach should be influenced by individual patient factors. In addition, immunosuppressive agents, including cyclophosphamide [up to 2 mg/kg/day (oral) for 3–6 months; or intermittent 15 mg/kg (IV) every 2 weeks for 3 doses, followed by 15 mg/kg (IV) every 3 weeks for at least 3 doses] or rituximab [375 mg/m^2 (IV) weekly for 4 doses or 1000 mg on days 1 and 15], are recommended in ACR guidelines. The comparative effectiveness of cyclophosphamide and rituximab for EGPA is unknown. For patients with SCr > 5.7 mg/dL (500 mmol/L) requiring dialysis or with rapidly increasing SCr, we need to consider plasma exchange (seven treatments over a maximum of 14 days, 60 ml/kg volume replacement, albumin substitution). The Methylprednisolone Versus Plasma Exchange for Renal Vasculitis (MEPEX) trial showed improved kidney outcomes in patients with severe kidney disease (SCr > 5.7 mg/dL [> 500 mmol/L]) who were treated with plasma exchange [9] (Figs. 1, 2).

After induction of remission, either rituximab (500 mg (IV) every 6 months or 1 g (IV) every 4 months) or azathioprine (up to 2 mg/kg/day) and low-dose glucocorticoids are recommended as maintenance therapy according to KDIGO guidelines (Table 1).

Conclusions

We started rituximab in combination with glucocorticoids as induction therapy because cyclophosphamide is associated with potentially severe side effects [10]. In our case, the patient denied the administration of cyclophosphamide. We used plasma exchange because her creatinine was increasing rapidly. Case reports identify a benefit of plasma exchange for the treatment of corticosteroid-refractory EGPA with gastrointestinal manifestations [11], however, there are no data investigating the role of plasma exchange in the management of renal manifestations of EGPA because the renal disease is extremely rare in EGPA. While there are several reports on the combination of rituximab and PE to treat other type of ANCA-associated vasculitis such as GPA [12], the regimen for this concurrent use varies among institutes. This case study suggests that the use of rituximab and concurrent PE may represent a promising combination for renal involvement of EGPA. However, further studies are needed to confirm the efficacy and optimal dosing schedule for this combination therapy.

Abbreviations

EGPA	Eosinophilic granulomatosis with polyangiitis
MPO-ANCA	Myeloperoxidase antineutrophil cytoplasmic antibody
CT	Computed tomography
LDL-cholesterol	Low-density lipoprotein
PE	Plasma exchange
GPA	Granulomatosis with polyangiitis

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Competing interests
The authors declare that they have no competing interests.

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