Case Report
Eosinophilic granulomatosis with polyangiitis and advanced renal failure in a case of glomerulosclerosis

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Abstract: A 33-year-old man was admitted with marked eosinophilia and advanced renal failure. Although he tested negative for myeloperoxidase and proteinase 3, he had a history of asthma, reversible pulmonary infiltration, diffuse sinusitis, and sensorimotor polyneuropathy. A renal biopsy demonstrated glomerulosclerosis. Eosinophilic granulomatosis with polyangiitis (EGPA) was diagnosed. Steroid and cyclophosphamide treatment induced symptom remission, eosinophil count normalization, and cardiac function recovery, but the renal dysfunction was not reversed. The patient is now in good condition with regular peritoneal dialysis. Here we report a rare case of glomerulosclerosis in a patient with EGPA.

Keywords: Eosinophilic granulomatosis with polyangiitis, glomerulosclerosis, antineutrophil cytoplasmic antibodies

Introduction
Eosinophilic granulomatosis with polyangiitis (EGPA) is a necrotizing vasculitis affecting small- to medium-sized vessels and eosinophil-rich granulomas involving the respiratory tract, and is associated with asthma and eosinophilia [1]. EGPA often affects the kidney in the form of pauci-immune crescentic glomerulonephritis [2]. Renal involvement is usually of mild to moderate degree, whereas advanced renal failure is uncommon. Here we report a case of a patient with antineutrophil cytoplasmic antibody (ANCA)-negative EGPA who initially presented with advanced renal failure and was diagnosed with glomerulosclerosis by biopsy.

Case
A 33-year-old man was admitted to our hospital in January 2013 with a 2-week history of fatigue and epistaxis after eating seafood. He had a history of asthma and denied a history of hypertension. On admission, his vitals included a blood pressure of 140/80 mmHg, pulse of 84/min, and respiratory rate of 18/min. Physical examination revealed 3+ pitting edema in the lower extremities. No obvious weight loss or skin lesions were observed. Laboratory findings were as follows: white blood cell count, 8.48×10³/μL; eosinophils, 17% (1410 cells/μL); hemoglobin, 70 g/dL; platelets, 192×10³/μL; total protein, 5.4 g/dL; serum albumin, 3.0 g/dL; serum urea nitrogen, 141.4 mg/dL; serum creatinine, 25.5 mg/dL; creatinine clearance, 4.0 mL/min; and C-reactive protein, 2.6 mg/dL. Cytoplasmic ANCA, perinuclear ANCA (p-ANCA), myeloperoxidase, and proteinase 3 were negative on immunofluorescence testing. Anti-DNA antibody, antinuclear antibody, anti-glomerular basement membrane antibody, and cryoglobulin were also undetected. Complement values were normal. Hepatitis B and C serology were negative. The 24-hour urinary protein excretion was 2.6 g. FIP1L1-PDGFRα fusion gene examination was negative.

Echocardiography revealed an ejection fraction of 64% on admission that gradually decreased to 35% 1 month later. Pleural effusion and ground glass opacities in the upper lobes of both lungs and the middle lobe of the right lung were noted on chest computed tomography (CT). Cytological examination of the hydrothorax revealed marked elevation of the eosinophil count. A CT scan of the head showed thickened nasal mucosa; isodense and homogeneous tissue occupied part of the right maxillary sinuses.
Electroneurography disclosed sensorimotor polyneuropathy with signs of axonal damage affecting the peroneal and tibial nerves. No nodular changes or aneurysms were seen on a renal angiogram.

A renal biopsy was performed. Light microscopy of the specimen demonstrated full or partial sclerosis of 12 glomeruli. Severe mesangial expansion with mesangial proliferation was found. Capsular adhesion was seen, but no crescents were observed. The tubules were diffusively atrophic, and interstitium was moderately to severely fibrotic with diffusive lymphocyte infiltration. Eosinophil infiltration was minimal. Fibrinoid necrosis, hyalinosis, and inflammatory cell infiltration in the wall of small vessels were seen. The capillary membranes were thickened and the capillary luminas were partially obliterated (Figure 2). Focal immunoglobulin A and C3 depositions in the mesangial area were observed by immunofluorescent staining, and we diagnosed the patient with glomerulosclerosis. EGPA was diagnosed according to the above clinical and laboratory findings.

The patient received peritoneal dialysis (PD) after admission and then was treated with a combination of oral prednisolone (60 mg/day) and pulse intravenous cyclophosphamide (750 mg/m²) 1 month later. After 4 weeks of treatment, the eosinophil count decreased to normal, pleural effusion and ground glass opacities on CT disappeared, and cardiac failure resolved, but the renal dysfunction could not be relieved. The patient’s creatinine clearance remained at < 15.0 mL/min. The patient is currently undergoing a regimen of six total doses of monthly iv cyclophosphamide 0.5 g/m² and...
EGPA in a case of glomerulosclerosis

low-dose oral prednisolone on alternating days and remains in good condition on PD (Figure 3).

Discussion

EGPA, known as allergic granulomatosis and angiitis, is characterized by classic histopathological findings of vasculitis and necrotizing extravascular granulomas with eosinophilic infiltration [1]. The American College of Rheumatology has established six diagnostic criteria for EGPA: asthma, eosinophilia > 10% on a differential white blood cell count, mononeuropathy (including mononeuritis multiplex) or polyneuropathy, non-fixed pulmonary infiltrates on chest X-rays, paranasal sinus abnormality, and the presence of extravascular eosinophils on a biopsy containing a blood vessel. The presence of four or more of these six criteria yielded a sensitivity of 85% and a specificity of 99.7% [3]. In this case, EGPA was diagnosed based on the findings of asthma, eosinophilia, sinusitis, polyneuropathy, reversible pulmonary infiltrates on chest CT, and pathological changes in the renal tissue.

The differential diagnosis of EGPA from hyper-eosinophilic syndrome (HES) is established by allergic history, pathological changes of vasculitis on a renal biopsy specimen, and negative FIP1L1-PDGFRα fusion gene. Examination of a bone marrow biopsy ruled out the possibility of HES caused by eosinophilic leukemia. Reactive HES, including helminthiasis and drug reactions, granulomatosis with polyangiitis (Wegener’s) and microscopic polyangiitis, and chronic eosinophilic pneumonia were also carefully ruled out. Negative radiological changes on a renal angiogram excluded polyarteritis nodosa.

Renal involvement occurred in 26-88% of patients with EGPA [4-6]. Necrotizing crescentic glomerulonephritis is the most common renal histological finding [7]. Other forms of renal diseases including eosinophilic tubulointerstitial nephritis, extracapillary proliferation, focal mesangial proliferative glomerulonephritis, focal segmental glomerular sclerosis, and membranous glomerulonephritis have also been reported [7-9]. Our patient presented with
advanced renal failure and biopsy-proven glomerulosclerosis and was ANCA-negative, which is a rare clinical manifestation of renal involvement in EGPA and has not been reported to our knowledge to date.

ANCA are present in approximately 40-60% of patients with EGPA; p-ANCA is the prevalent pattern, with antibody specificity for MPO [10]. The most plausible subclassification contrasts ANCA-positive EGPA, characterized by manifestations resulting from small- and medium-sized vessel vasculitis and ANCA-negative EGPA, in which the organs primarily damaged by eosinophilic infiltration. These subsets are not clearly separated, as overlapping manifestations occur very frequently. Whether patients with ANCA-negative and -positive EGPA indeed represent the same disease entity is debatable. Previous investigations discovered that the frequency of necrotizing crescentic glomerulonephritis is significantly increased in patients with ANCA-positive EGPA [7, 10]. In ANCA-negative cases, tissue infiltration by eosinophils is the histopathological hallmark, and the release of toxic products from eosinophils might be the main pathogenic mechanism [11]. The renal pathological findings of our patient included minimal eosinophil infiltration without granulation, and no crescents or necrotizing glomerulonephritis was seen, probably due to the absence of ANCA. However, the possibility of concurrent idiopathic glomerulosclerosis and EGPA cannot be completely ruled out. This patient developed advanced renal failure and glomerulosclerosis within a short time, suggesting that renal involvement in ANCA-negative EGPA is dormant but can progress rapidly. As a result of negative ANCA, such patients with EGPA are more likely to be misdiagnosed and experience treatment delays.

EGPA treatment is under debate because of a lack of large-scale randomized controlled trials, including corticosteroid, cyclophosphamide, azathioprine or methotrexate, mycophenolate mofetil, and B-cell depletion adjunct therapy with rituximab. The five factors score (FFS) may be a guide for clinicians since it assigns one point to each of the following items, namely gastrointestinal involvement, central nervous system involvement, cardiac involvement, proteinuria > 1 g/24 h, and serum creatinine > 141 mmol/L [12]. Patients with poor prognosis (FFS ≥ 1) are often treated with both glucocorticoids and cyclophosphamide, while glucocorticoid therapy alone, the typical approach for patients with a better prognosis (e.g., FFS of 0). Since our patient had an FFS of 3, we treated him as a case with high severity. Although our patient’s renal function was not recovered after immunosuppressive therapy, other clinical conditions were markedly improved, especially cardiac involvement, which is a major cause of morbidity and mortality in patients with EGPA [13]. We were not able to perform a myocardial tissue biopsy to obtain direct evidence of eosinophilic infiltration, but the improvement in cardiac function after the glucocorticoid treatment indirectly confirmed it.

Our findings suggest that the early detection of EGPA should be performed, especially in patients with ANCA-negative EGPA, and treatment consisting of glucocorticoids combined with immunosuppressants might improve outcomes in severe cases.

Disclosure of conflict of interest

None.

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References


EGPA in a case of glomerulosclerosis


