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Renal Involvement in Eosinophilic Granulomatosis With Polyangiitis

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INTRODUCTION

Eosinophilic granulomatosis with polyangiitis (EGPA), previously called Churg–Strauss syndrome, is a small- to medium-sized systemic necrotizing vasculitis characterized by eosinophil-rich tissue infiltrates and granulomatous lesions. Eosinophilic granulomatosis with polyangiitis belongs to the larger subgroup of anti-neutrophil cytoplasm antibodies (ANCA)–associated vasculitides. However, EGPA is characterized by a distinct biological and clinical presentation when compared with granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA). It is typically characterized by late-onset asthma, nasal and sinus-related symptoms, peripheral neuropathy, and prominent peripheral blood eosinophilia.[1] The prevalence of ANCA positivity in EGPA is about 40%, with predominant perinuclear staining, and exhibits an anti-MPO specificity in approximatively 65% of cases.[1,2] Unlike GPA and MPA, in which kidney involvement is a central feature, nephropathy is not considered a prominent aspect in patients with EGPA.[1,3] For this reason, the nephrologist is not usually regarded as a key player in the care of EGPA patients. The case reported here dispels this misconception by demonstrating that, in selected cases, nephrological expertise may play an active role in patient management.

CASE PRESENTATION

Clinical History and Laboratory Data at Presentation

A 63-year-old man was referred to our department for stage 3 Kidney Disease: Improving Global Outcomes (KDIGO) acute kidney injury. His preceding history was consistent for late-onset asthma, with initial symptoms occurring 20 years earlier, recurrent nasal polyposis with anosmia, and uncomplicated type 2 diabetes. He had evidence of transient eosinophilia (blood eosinophil count, 1.4 × 10^9/l; normal range, 0.03–0.7) 3 years prior to his referral. Upon admission, the patient reported fatigue, loss of weight, and muscle weakness, predominantly in the lower limbs. In addition, he described nasal crusting obstruction.

Biological investigations showed eosinophilia (7.4 × 10^9/l) and stage 3 KDIGO acute kidney injury with a serum creatinine level of 360 μmol/l (normal range: 45–97), compared to 110 μmol/l twelve months earlier. Urine protein/creatinine ratio was 1.1 g/g (normal range, 0–30), with 0.6 g/g albuminuria. The patient presented with microscopic hematuria (urine red blood cell count 113,000/ml; normal range, <10,000/ml). Anti-neutrophil cytoplasm antibodies were positive with perinuclear fluorescence (1/640, normal range, <1/20). An enzyme-linked immunosorbent assay demonstrated elevated ANCA specific for myeloperoxidase (82 IU/ml; normal range, <20).

Kidney Biopsy Findings

The kidney biopsy specimen showed 7 glomeruli, 4 of which had active necrotizing glomerulonephritis, segmental fibrinoid necrosis, and rupture of the glomerular basement membrane (Figure 1A). Interstitial fibrosis was moderate, with numerous foci of interstitial eosinophil polymorphonuclear leucocytes (Figure 1B). No interstitial granuloma was found. The specimen contained an unremarkable artery. An

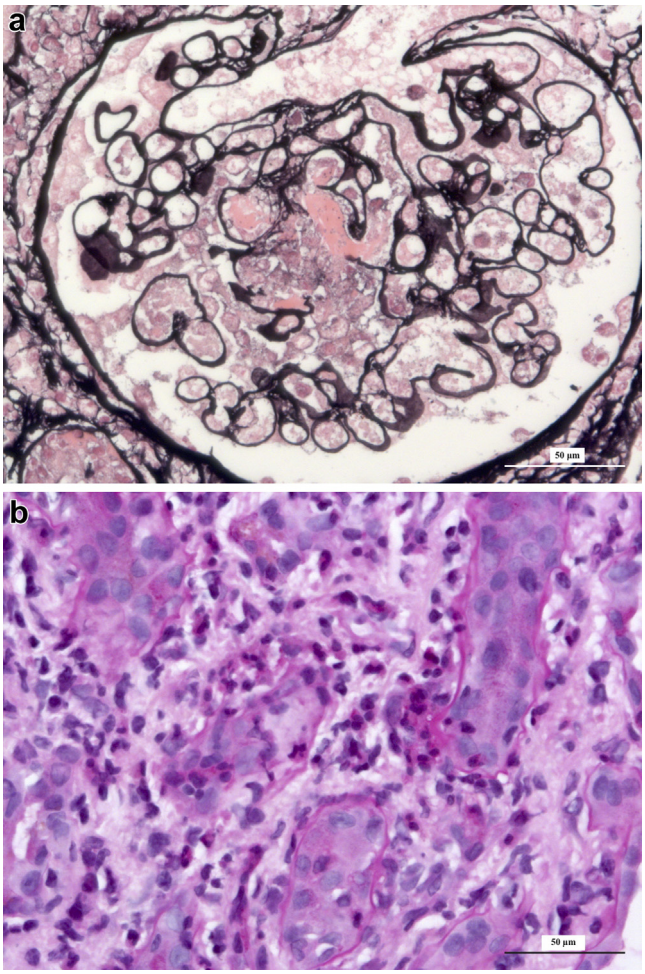

Figure 1. Kidney biopsy findings. (a) Active necrotizing glomerulonephritis showing fibrin deposits and segmental glomerular basement membrane rupture on light microscopy (original magnification x400, Jones methenamine silver stain). (b) Eosinophil-rich interstitial inflammation on light microscopy (original magnification x400, hematoxylin–eosin–saffron).

immunofluorescence study yielded no deposit. Electron microscopy was not performed.

The diagnosis of eosinophilic granulomatosis with polyangiitis with renal involvement was proposed.

Treatment and Clinical Follow-up

The patient was treated with a pulse of methylprednisolone 500 mg daily for 3 days, followed by oral prednisone 1 mg/kg and i.v. cyclophosphamide 0.5 mg/m^2 (day 1, day 15, day 29, and then every 21 days for a total of 6 pulses). Seven sessions of plasmatic exchange over a 10-day period were initiated after the histopathological examination results were known. Hyper-eosinophilia receded from 7.4 × 10^9/l to 0.6 × 10^9/l the day after the initial steroid pulse. Peripheral blood eosinophilia had resolved 4 months after the initial follow-up. Renal function improved gradually within 10 days after the initiation of the induction treatment to reach a serum creatinine plateau of 140 μmol/l (estimated glomerular filtration rate of 46 ml/min per 1.73 m^2 according to the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] formula). At the final follow-up, residual proteinuria was still present, at around 1 g/g, whereas hematuria was not detected.

DISCUSSION

Kidney disease ranks among the most prominent clinical characteristic of ANCA-associated vasculitis. Of the patients with GPA, 70% display signs of renal involvement, whereas it is a near-universal feature of patients with MPA. Nephrologists are perhaps less familiar with EGPA. However, intrinsic renal injury is, in fact, not uncommon, and has been recorded in up to 25% of patients affected by EGPA.[1,4]

As epitomized by the patient's history, EGPA typically follows 3 sequential stages: first, a prodromal phase characterized by atopic disease, allergic rhinitis, and asthma, followed by a second eosinophilic phase defined by peripheral blood eosinophilia and eosinophilic infiltration of multiple organs, and finally a vasculitic stage marked by life-threatening systemic vasculitis affecting medium and small vessels. The prodromal phase usually precedes the vasculitic phase by approximately 10 years.[1,5] The ANCA status represents the overriding determinant that dictates the clinical profile: ANCA-positive patients tend to display vasculitis-related symptoms including kidney disease and peripheral nerve involvement, whereas ANCA-negative patients are more prone to develop complications in connection with eosinophilia.[2] Renal disease in EGPA is closely associated with ANCA positivity.[1,2,4] Indeed, patients with positive ANCA account for 80% of EGPA patients with renal involvement, although they represent less than 40% of all patients in most EGPA series.[1,4]

Necrotizing pauci-immune glomerulonephritis is the most common renal presentation, found in 88% of ANCA-positive EGPA cases with renal involvement.[4] Compared to MPA and GPA vasculitis, in which kidney disease is frequently diagnosed at advanced stages, most EGPA patients with rapidly progressive glomerulonephritis exhibit crescentic lesions, reflecting recent and acute insult. This pattern of renal injury may translate to an early recognition of renal disease heralded by demonstrative EGPA-associated extrarenal symptoms. More than half of EGPA biopsy specimens displaying necrotizing crescentic glomerulonephritis also yielded prominent acute interstitial inflammation, composed mainly of eosinophilic polymorphonuclear cells. The interstitial inflammation is also a usual

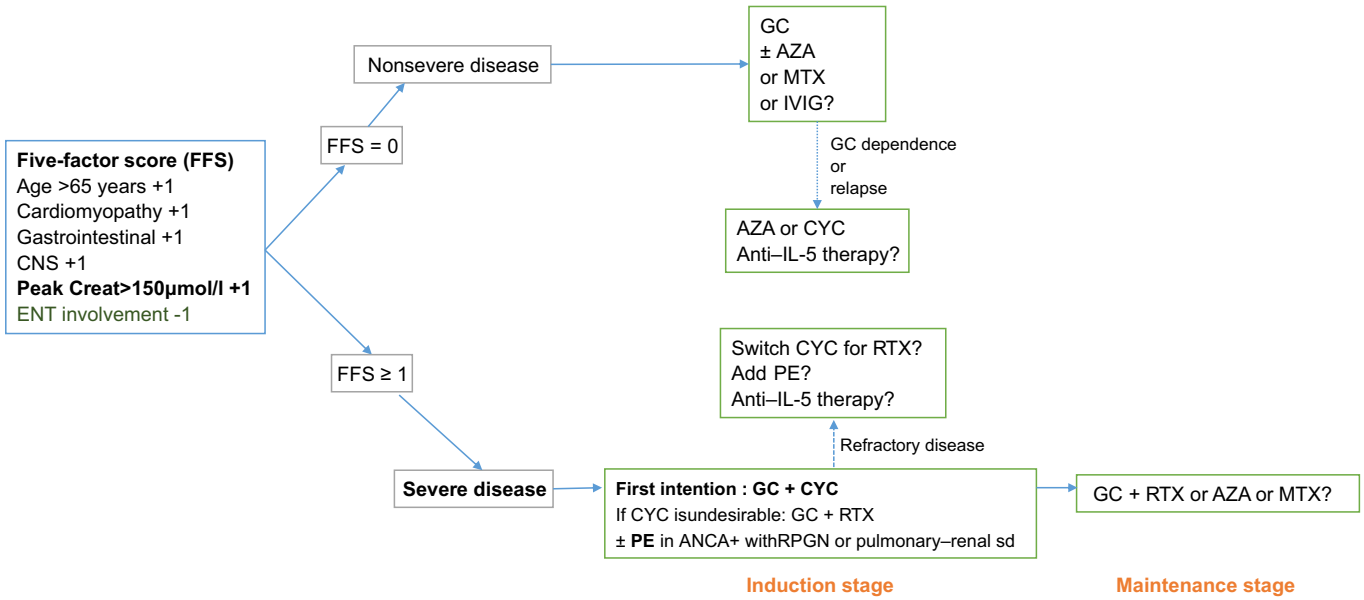

Figure 2. Summary of therapeutic options in EGPA according to disease severity. "Five-factor score" is established by computing the algebraic sum related to each organ-related EGPA manifestation. Therapeutic options consistent with renal involvement appear in bold characters; question mark indicates treatment option that may be considered based on limited studies and/or ongoing studies. AZA, azathioprine; CNS, central nervous system; CYC, cyclophosphamide (intravenous or oral); EGPA, eosinophilic granulomatosis with polyangiitis; ENT, ear—nose—throat; FFS, five-factor score; GC, glucocorticoids; IVIG, intravenous immunoglobulins; MTX, methotrexate; PE, plasmapheresis; RPGN, rapidly progressive glomerulonephritis; RTX, rituximab.

feature in GPA or MPA patients, but consists mainly of T- and B-lymphocytes, sometimes associated with plasma cells.[6] Inflammatory cells may also aggregate into granuloma, albeit very infrequently in an EGPA kidney biopsy specimen, where it has been documented in only 5% of cases.[4] The case presented here encapsulates the histopathological hallmarks of renal involvement of the disease, and serves as an illustration of the dual mechanisms of EGPA lesions whereby both eosinophilic organ infiltration (phase 2) and vasculitis with necrotizing glomerulonephritis are observed (phase 3). At any rate, acute kidney injury predicts poor prognosis and should warrant combined immunosuppressive therapy, typically an association of glucocorticoids and cyclophosphamide, to prevent the risk of severe chronic kidney disease (Figure 2).[7]

The EGPA patients who are ANCA negative seldom display renal involvement, yet atypical glomerular disease has recently been established. Durel *et al*. documented cases of membranoproliferative and membranous nephropathy among ANCA-negative EGPA patients.[4] The coexistence of membranous nephropathy and EGPA could be more than an accidental finding, considering that both diseases may share a common genetic background with common HLA alleles involved in both EGPA and membranous nephropathy.[8] Moreover, ANCA-negative EGPA patients are characterized by a Th2-weighted pro-inflammatory response, akin to that of patients with membranous nephropathy.[8] Nevertheless, the connection between EGPA and membranous or membranoproliferative nephropathies needs to be substantiated by further studies.

This case, together with recent evidence, is at odds with a popular belief stemming from earlier works, according to which renal disease in the context of EGPA is mild and follows a benign course.[9] Even if the diagnosis of renal disease is usually made early in EGPA, renal involvement is far from inconsequential, with nearly 20% of patients reaching end-stage renal disease within 4 years of follow-up.[4] Renal vasculitis therefore remains a severe complication in all forms of ANCA-associated vasculitides, and EGPA is no exception. A summary of learning points can be found in Table 1.

Table 1. Teaching points

- Eosinophilic granulomatosis with polyangiitis (EGPA) patients exhibit renal involvement in nearly a quarter of cases.
- The frequency of renal involvement and its histopathological manifestations is driven by anti-neutrophil cytoplasm antibodies (ANCA) status:
  - The great majority of EGPA patients with renal involvement are ANCA positive;
  - Necrotizing pauci-immune glomerulonephritis is the most common renal presentation in ANCA-positive EGPA;
  - Significant eosinophilic interstitial inflammation is found in half of the cases;
  - Renal involvement is infrequent in ANCA-negative EGPA, and atypical renal presentation may occur.
- The course of renal disease in EGPA may be severe and should be managed accordingly.

DISCLOSURE

All the authors declared no competing interests.

PATIENT CONSENT

The authors declare that they have obtained consent from the patient discussed in the report.

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