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1 **Renal involvement in eosinophilic granulomatosis with polyangiitis**

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1 **Introduction**

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

15 **The Case**

16 **Clinical History and Laboratory Data at Presentation**

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

23 Biological investigations showed eosinophilia ($7.4 \times 10^9/l$) and stage 3 KDIGO acute kidney injury
24 with a serum creatinine level of 360 $\mu\text{mol/l}$ (normal range: 45–97), compared to 110 $\mu\text{mol/l}$ twelve
25 months earlier. The urine protein/creatinine ratio was 1.1 g/g (normal range: 0–30), with 0.6 g/g
26 albuminuria. The patient presented with microscopic hematuria (urine RBC 113000/ml, normal range:
27 $<10000/ml$). Anti-neutrophil cytoplasm antibodies (ANCA) were positive with perinuclear
28 fluorescence (1/640, normal range: $< 1/20$). An enzyme-linked immunosorbent assay demonstrated
29 elevated ANCA specific for myeloperoxidase (82 IU/ml, normal range: < 20).

30 **Kidney Biopsy Specimen**

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

1 unremarkable artery. Immunofluorescence study yielded no deposit. Electron microscopy was not
2 performed.

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

4 **Treatment and Clinical Follow-up**

5 The patient was treated with a pulse of methylprednisolone 500 mg daily for three days, followed by
6 oral prednisone 1 mg/kg, intravenous cyclophosphamide 0.5 mg/m² (day 1, day 15, day 29 and then
7 every 21 days for a total of 6 pulses). Seven sessions of plasmatic exchange over a 10-day period were
8 initiated after the histopathological examination results were known. Hyper-eosinophilia receded from
9 $7.4 \times 10^9/l$ to $0.6 \times 10^9/l$ the day after the initial steroid pulse. Peripheral blood eosinophilia had
10 resolved four months after initial follow-up. Renal function improved gradually within ten days after
11 the initiation of the induction treatment to reach a serum creatinine plateau of 140 $\mu\text{mol/l}$ (estimated
12 glomerular filtration rate of 46 ml/min/1.73m² according to the CKD-EPI formula). At final follow-up,
13 residual proteinuria was still present, at around 1 g/g, whereas hematuria was not detected.

14 **Discussion**

15 Kidney disease ranks among the most prominent clinical characteristic of ANCA-associated vasculitis.
16 Seventy percent of the patients with GPA display signs of renal involvement while it is a near-
17 universal feature of patients with MPA. Nephrologists are perhaps less familiar with EGPA. However,
18 intrinsic renal injury is in fact not uncommon, and has been recorded in up to 25% of patients affected
19 by EGPA.^{1,4}

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

31 Necrotizing pauci-immune glomerulonephritis is the most common renal presentation, found in 88%
32 of ANCA-positive EGPA cases with renal involvement.⁴ Compared to MPA and GPA vasculitis,
33 where kidney disease is frequently diagnosed at advanced stages, most EGPA patients with rapidly

1 progressive glomerulonephritis exhibit crescentic lesions, reflecting recent and acute insult. This
2 pattern of renal injury may translate to an early recognition of renal disease heralded by demonstrative
3 EGPA-associated extra-renal symptoms. More than half of EGPA biopsies displaying necrotizing
4 crescentic glomerulonephritis also yielded prominent acute interstitial inflammation, mainly composed
5 of eosinophilic polymorphonuclear cells. The interstitial inflammation is also a usual feature in GPA
6 or MPA patients, but consists mainly of T- and B-lymphocytes, sometimes associated with plasma
7 cells.⁶ Inflammatory cells may also aggregate into granuloma, albeit very infrequently in an EGPA
8 kidney biopsy, where it has been documented in only 5% of cases.⁴ The case presented here
9 encapsulates the histopathological hallmarks of renal involvement of the disease and serves as an
10 illustration of the dual mechanisms of EGPA lesions whereby both eosinophilic organ infiltration
11 (phase 2) and vasculitis with necrotizing glomerulonephritis are observed (phase 3). At any rate, acute
12 kidney injury predicts poor prognosis and should warrant combined immunosuppressive therapy,
13 typically an association of glucocorticoids and cyclophosphamide, to prevent the risk of severe chronic
14 kidney disease (Figure 2).⁷

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

24
25 This case, together with recent evidence, is at odds with a popular belief stemming from earlier works
26 according to which renal disease in the context of EGPA is mild and follows a benign course.⁹ Even if
27 the diagnosis of renal disease is usually made early in EGPA, renal involvement is far from
28 inconsequential, with nearly 20% of patients reaching end stage renal disease within four years of
29 follow-up.⁴ Renal vasculitis therefore remains a severe complication in all forms of AAV, and EGPA
30 is no exception. A summary of learning points can be found in Table 1.

31

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1 Table 1. Teaching points

2

- 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 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.

3 Figures legends**4 Figure 1: Kidney biopsy findings**

5 **A.** Active necrotizing glomerulonephritis showing fibrin deposits and segmental glomerular basement
6 membrane rupture at light microscopy (original magnification x 400, Jones methenamine silver stain)

7 **B.** Eosinophil-rich interstitial inflammation at light microscopy (original magnification x 400,
8 hematoxylin-eosin-saffron)

9 Figure 2: Summary of therapeutic options in EGPA according to disease severity

10 AZA: azathioprine, CYC: cyclophosphamide (intravenous or oral), CNS: central nervous system,
11 EGPA: eosinophilic granulomatosis with polyangiitis, ENT: ear nose throat, GC: glucocorticoids,
12 IVIG: intravenous immunoglobulins, MTX: methotrexate, PE: plasmapheresis, RTX: rituximab,
13 RPGN: rapidly progressive glomerulonephritis

14 Five factor score is established by computing the algebraic sum related to each organ-related EGPA
15 manifestation

16 Therapeutic options consistent with renal involvement appear in bold characters, question mark
17 indicates treatment option that may be considered based on limited studies and/or ongoing studies.

18



