



**HAL**  
open science

## Renal involvement in eosinophilic granulomatosis with polyangiitis

Alice Doreille, David Buob, Pierre Bay, Marie Julien, Frédéric Riviere, Cédric Rafat

► **To cite this version:**

Alice Doreille, David Buob, Pierre Bay, Marie Julien, Frédéric Riviere, et al. Renal involvement in eosinophilic granulomatosis with polyangiitis. *Kidney International Reports*, 2021, 10.1016/j.ekir.2021.07.002 . hal-03292012

**HAL Id: hal-03292012**

<https://hal.sorbonne-universite.fr/hal-03292012v1>

Submitted on 20 Jul 2021

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

# Journal Pre-proof

Renal involvement in eosinophilic granulomatosis with polyangiitis

Alice Doreille, David Buob, Pierre Bay, Marie Julien, Frédéric Riviere, Cédric Rafat



PII: S2468-0249(21)01296-1

DOI: <https://doi.org/10.1016/j.ekir.2021.07.002>

Reference: EKIR 1554

To appear in: *Kidney International Reports*

Received Date: 25 May 2021

Revised Date: 1 July 2021

Accepted Date: 3 July 2021

Please cite this article as: Doreille A, Buob D, Bay P, Julien M, Riviere F, Rafat C, Renal involvement in eosinophilic granulomatosis with polyangiitis, *Kidney International Reports* (2021), doi: <https://doi.org/10.1016/j.ekir.2021.07.002>.

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2021 Published by Elsevier Inc. on behalf of the International Society of Nephrology.

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

2 Alice DOREILLE<sup>1,2</sup>, David BUOB<sup>2,3</sup>, Pierre BAY<sup>1</sup>, Marie JULIEN<sup>1</sup>, Frédéric RIVIERE<sup>4</sup>, Cédric  
3 RAFAT<sup>1</sup>

4 <sup>1</sup> Assistance Publique Hopitaux de Paris, Nephrology Intensive Care Unit, Tenon hospital, Paris, Ile de  
5 France, France

6 <sup>2</sup> Sorbonne Université Paris, Ile de France, France

7 <sup>3</sup> Assistance Publique - Hopitaux de Paris, Pathology department, Tenon Hospital, Paris, Île-de-  
8 France, France

9 <sup>4</sup> Hôpital d'Instruction des Armées Percy, Pulmonology department, Clamart, Ile de France, France

10 Corresponding author:

11 Alice DOREILLE

12 Nephrology Intensive Care Unit, Tenon hospital, 4 rue de la Chine, 75020 Paris, France

13 alice.doreille@aphp.fr

14 + 33 1 56 01 65 03

15

16 **Word count: 1179/1200**

17 **Disclosures:** All the authors declared no competing interests.

18 **Patient Consent:** The authors declare that they have obtained consent from the patient discussed in  
19 the report.

20

21

## 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.<sup>1</sup> 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.<sup>1,2</sup> Unlike GPA and MPA, where kidney involvement is a central  
11 feature, nephropathy is not considered a prominent aspect in patients with EGPA.<sup>1,3</sup> 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/m<sup>2</sup> (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/1.73m<sup>2</sup> 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.<sup>1,4</sup>

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.<sup>1,5</sup> 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.<sup>2</sup> Renal disease in EGPA is closely associated with  
29 ANCA positivity.<sup>1,2,4</sup> 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.<sup>1,4</sup>

31 Necrotizing pauci-immune glomerulonephritis is the most common renal presentation, found in 88%  
32 of ANCA-positive EGPA cases with renal involvement.<sup>4</sup> 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.<sup>6</sup> 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.<sup>4</sup> 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).<sup>7</sup>

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.<sup>4</sup> 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.<sup>8</sup> Moreover, ANCA-negative EGPA patients are characterized by a Th2-weighted pro-  
21 inflammatory response, akin to that of patients with membranous nephropathy.<sup>8</sup> 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.<sup>9</sup> 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.<sup>4</sup> 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

## 1   **References**

- 2   1.     Comarmond C, Pagnoux C, Khellaf M, et al. Eosinophilic granulomatosis with  
3   polyangiitis (Churg-Strauss): clinical characteristics and long-term followup of the 383  
4   patients enrolled in the French Vasculitis Study Group cohort. *Arthritis Rheum.*  
5   2013;65(1):270-281. doi:10.1002/art.37721
- 6   2.     Sinico RA, Di Toma L, Maggiore U, et al. Prevalence and clinical significance of  
7   antineutrophil cytoplasmic antibodies in Churg-Strauss syndrome. *Arthritis Rheum.*  
8   2005;52(9):2926-2935. doi:10.1002/art.21250
- 9   3.     Sinico RA, Di Toma L, Maggiore U, et al. Renal involvement in Churg-Strauss  
10   syndrome. *Am J Kidney Dis Off J Natl Kidney Found.* 2006;47(5):770-779.  
11   doi:10.1053/j.ajkd.2006.01.026
- 12   4.     Durel C-A, Sinico RA, Teixeira V, et al. Renal involvement in eosinophilic  
13   granulomatosis with polyangiitis (EGPA): a multicentric retrospective study of 63 biopsy-  
14   proven cases. *Rheumatol Oxf Engl.* 2021;60(1):359-365. doi:10.1093/rheumatology/keaa416
- 15   5.     Guillevin L, Cohen P, Gayraud M, Lhote F, Jarrousse B, Casassus P. Churg-Strauss  
16   syndrome. Clinical study and long-term follow-up of 96 patients. *Medicine (Baltimore).*  
17   1999;78(1):26-37. doi:10.1097/00005792-199901000-00003
- 18   6.     Berden AE, Ferrario F, Hagen EC, et al. Histopathologic classification of ANCA-  
19   associated glomerulonephritis. *J Am Soc Nephrol JASN.* 2010;21(10):1628-1636.  
20   doi:10.1681/ASN.2010050477
- 21   7.     Groh M, Pagnoux C, Baldini C, et al. Eosinophilic granulomatosis with polyangiitis  
22   (Churg-Strauss) (EGPA) Consensus Task Force recommendations for evaluation and  
23   management. *Eur J Intern Med.* 2015;26(7):545-553. doi:10.1016/j.ejim.2015.04.022
- 24   8.     Kronbichler A, Bettac EL. Kidney disease in eosinophilic granulomatosis with  
25   polyangiitis: expect the unexpected. *Rheumatol Oxf Engl.* 2021;60(1):1-2.  
26   doi:10.1093/rheumatology/keaa571
- 27   9.     Lanham JG, Elkon KB, Pusey CD, Hughes GR. Systemic vasculitis with asthma and  
28   eosinophilia: a clinical approach to the Churg-Strauss syndrome. *Medicine (Baltimore).*  
29   1984;63(2):65-81. doi:10.1097/00005792-198403000-00001

## 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





