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# From Asymptomatic Myeloperoxidase-Antineutrophil Cytoplasmic Antibody (MPO-ANCA) Seropositivity to Crescentic Glomerulonephritis and Cold Agglutinin Disease Following Chlamydia Infection: A Second-Hit Hypothesis

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## Abstract

Myeloperoxidase (MPO)-antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a recognised cause of rapidly progressive glomerulonephritis (GN), while cold agglutinin disease (CAD) is a rare autoimmune haemolytic disorder that is frequently associated with infections. The simultaneous occurrence of MPO-ANCA GN and CAD is uncommon and presents significant diagnostic and therapeutic challenges.

We describe a patient with longstanding asymptomatic MPO-ANCA seropositivity who developed rapidly progressive renal dysfunction, active urinary sediment, and biopsy-proven crescentic GN in association with cold agglutinin-mediated haemolysis following a recent respiratory illness attributed to *Chlamydia pneumoniae* infection. This case suggests a second-hit mechanism in which *C. pneumoniae* may have contributed to the development of two immune-mediated processes in a susceptible host and highlights the importance of evaluating for infectious triggers when AAV presents with atypical haematological features.

**Categories:** Hematology, Nephrology

**Keywords:** anca-associated vasculitis, chlamydia pneumoniae, cold agglutinin disease, infection-triggered autoimmunity, second-hit hypothesis

## Introduction

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) comprises necrotising small-vessel vasculitis that, although historically defined by clinical syndromes such as granulomatosis with polyangiitis and microscopic polyangiitis, is increasingly more accurately stratified by ANCA serotype proteinase 3 (PR3) or myeloperoxidase (MPO) [1]. Clinical outcome data further show that antibody specificity correlates more strongly than phenotype with relapse propensity [2,3] and therapeutic response, particularly to rituximab [4]. PR3-ANCA and MPO-ANCA disease therefore represent biologically distinct entities within the AAV spectrum rather than merely serological variants of the same clinical syndromes.

However, autoantibody positivity does not inevitably equate to clinical autoimmune disease. In AAV, PR3- and MPO-ANCA may be detectable for years before the development of clinical manifestations, supporting the concept of a preclinical phase of silent autoimmunity. Biobank and case-control studies have demonstrated ANCA positivity in archived sera collected prior to symptom onset in patients who subsequently developed AAV [5]. Complement activation products and subtle inflammatory protein perturbations have also been detected in these presymptomatic samples, suggesting that silent seropositivity represents a state of low-grade immune activation rather than simple antibody carriage [6,7].

ANCA positivity has also been reported in patients with inflammatory bowel disease, rheumatoid arthritis, and other inflammatory conditions without vasculitis, many of whom do not progress to systemic disease [8]. These observations suggest that the presence of ANCA alone does not usually lead to clinical disease. The mechanisms underlying the transition from asymptomatic seropositivity or low-grade immune activation to overt necrotising vasculitis remain incompletely defined and likely involve additional inflammatory triggers, consistent with a second-hit hypothesis.

## Case Presentation

A 64-year-old woman was referred to the emergency department following blood tests arranged by her general practitioner, which showed severe anaemia and acute kidney injury. These tests had been requested

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because she had felt unwell and had shortness of breath for 7–10 days. Her past medical history included hypertension and subclinical hypothyroidism. Her regular medications were irbesartan, indapamide, amlodipine, and solifenacin.

On admission, haemoglobin was 58 g/L, with a normal white cell count and platelet count. Serum creatinine was elevated at 392 µmol/L. Erythropoietin levels were normal. Peripheral blood film demonstrated red cell agglutination. Direct antiglobulin testing (DAT) was strongly positive for C3d (+++) and negative for IgG, consistent with cold agglutinin-mediated haemolysis. The reticulocyte count was modestly elevated; bilirubin was normal on admission and became mildly elevated on day 3, while lactate dehydrogenase and haptoglobin remained normal. She required five units of red blood cells before her haemoglobin stabilised. Haematology considered the overall findings consistent with cold agglutinin disease (CAD).

Bone marrow aspirate showed no lymphoid excess, and trephine biopsy demonstrated no morphological evidence of lymphoma. Flow cytometry identified a small clonal B-cell population of approximately 1.5%, CD5-negative with weak CD23 expression. Serum free light chains were elevated but with a preserved kappa ratio of 1.11, and serum immunofixation detected no paraprotein.

Although flow cytometry identified a small clonal B-cell population, the absence of morphological evidence of lymphoma, a detectable serum paraprotein, or radiological evidence of lymphoproliferative disease meant that an overt clonal lymphoproliferative disorder was not established. Nevertheless, the clinical significance of the small clone remains uncertain. This was the haematology team's opinion. Also, repeat bone marrow assessment was suggested if the haematological abnormalities recur.

She had a respiratory PCR swab positive for *Chlamydia pneumoniae* and negative for *Mycoplasma pneumoniae*. Whole-body contrast-enhanced CT showed no evidence of lymphoproliferative disease or any other malignancy.

Review of historical laboratory records revealed MPO-ANCA positivity (31.0 IU/mL) approximately 10 years earlier, although the indication for testing was unclear. She remained asymptomatic, with preserved renal function, until the current presentation. During the current presentation in 2025, MPO-ANCA remained positive at 31.0 IU/mL and increased to 41.0 IU/mL on repeat testing. Other autoimmune and infectious screens were negative, and complement levels were within the normal range. Urine analysis showed haematuria and proteinuria.

Given the severe acute kidney injury, haematuria, proteinuria and positive MPO-ANCA serology, immunosuppressive treatment was initiated before kidney biopsy because of concern for active ANCA-associated glomerulonephritis (GN) and the potential risk of delaying treatment. Biopsy was deferred while the severe anaemia was addressed. The patient received intravenous methylprednisolone and one dose of cyclophosphamide before biopsy, with subsequent improvement in serum creatinine to 130 µmol/L.

Following clinical stabilisation, renal biopsy was done and confirmed pauci-immune crescentic GN. The renal biopsy contained 29 glomeruli, of which four were globally sclerosed. Three glomeruli showed cellular crescents, while 11 showed fibrocellular crescents. Segmental glomerulosclerosis and adhesions were also identified. The tubulointerstitium showed acute tubular injury with red-cell and granular casts, together with mild interstitial inflammation and tubulitis. Interstitial fibrosis and tubular atrophy involved approximately 15% of the sampled cortex. Immunofluorescence showed no significant specific staining for IgG, IgA, IgM, C3 or C1q, supporting a pauci-immune pattern of GN (Figure 1).

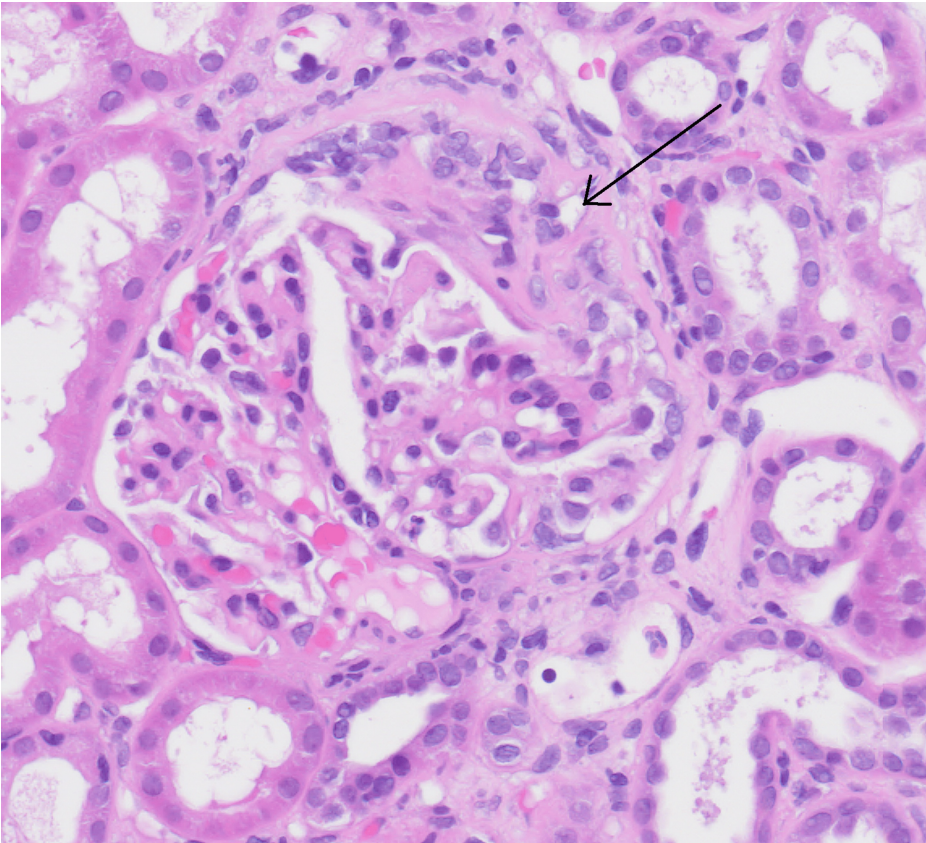


FIGURE 1: Renal biopsy showing crescentic glomerulonephritis in representative hematoxylin and eosin (H&E)-stained sections at ×40 magnification. The black arrow indicates crescentic lesions.

Induction treatment was continued with a further dose of cyclophosphamide and two doses of rituximab according to the departmental protocol. Combined cyclophosphamide and rituximab is an option recognised in the 2024 Kidney Disease: Improving Global Outcomes (KDIGO) guideline for selected patients with severe renal involvement [9]. Levofloxacin was administered for confirmed *C. pneumoniae* infection. Renal function and haemoglobin subsequently improved, with a last creatinine of 78 µmol/L (Table 1).

| Time point      | Clinical events/investigations                                                                                         | Treatment and response                                                                                    |
|-----------------|------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------|
| At presentation | Severe anaemia (Hb 58 g/L), acute kidney injury (creatinine 392 µmol/L), active urinary sediment and positive MPO-ANCA | Red blood cell transfusion                                                                                |
| Week 1          | Persistent acute kidney injury with positive MPO-ANCA                                                                  | Intravenous methylprednisolone commenced                                                                  |
| Week 2          | Respiratory PCR positive for <i>Chlamydia pneumoniae</i>                                                               | First dose of cyclophosphamide and levofloxacin commenced; creatinine subsequently improved to 130 µmol/L |
| Week 4          | Renal biopsy performed after clinical stabilisation, demonstrating pauci-immune crescentic glomerulonephritis          | Further immunosuppression with cyclophosphamide and rituximab                                             |
| Follow-up       | Continued clinical and haematological improvement                                                                      | Creatinine improved further to 78 µmol/L and haemoglobin stabilised                                       |

TABLE 1: Clinical and treatment timeline.

MPO: myeloperoxidase; ANCA: antineutrophil cytoplasmic antibody

## Discussion

Our patient had 10 years of silent MPO-ANCA seropositivity without any clinical vasculitis. Previous studies have shown that ANCA may precede clinical disease by months to a few years, with a median interval of two years reported in preclinical cohorts [6]. The 10-year interval in our case is unusual and supports the idea that ANCA seropositivity alone is not sufficient to cause clinical vasculitis. Persistent MPO-ANCA high titres over time with subsequent clinical conversion showed the limitation of the use of antibody levels in predicting disease onset [10].

Infection is thought to stimulate neutrophil priming and activation, leading to activation of the pathogenic pre-existing ANCA [11,12]. Inflammatory cytokines and complement activation play a role in neutrophil-mediated vascular injury [13]. In our view, this fits with the second hit hypothesis in disease pathogenesis, in which a trigger will be needed to prime autoantibodies to cause an overt disease.

Previous studies have suggested a possible association between *C. pneumoniae* and MPO-ANCA-associated GN. Iyoda et al. found higher anti-*C. pneumoniae* IgM in active MPO-ANCA GN than in controls (60% vs 26%; OR 4.27;  $P = 0.01$ ), with paired reductions in IgM and IgA indices during remission. Kawaguchi et al. similarly reported increased IgM seropositivity in MPO-ANCA GN compared with age-similar IgA nephropathy controls (39.4% vs 7.5%; adjusted OR 9.79;  $P = 0.001$ ) [14,15]. However, these serological findings are not uniform across studies and may be influenced by assay-related factors such as rheumatoid factor interference; using revised methods to reduce this, Ikenoya et al. reported lower IgM prevalence and concluded that an aetiological role remained unproven [16]. The use of PCR to detect *C. pneumoniae* in our patient confirms the presence of active infection. The temporal relationship between the respiratory illness and the subsequent renal and haematological manifestations raises the possibility of an infection-associated second-hit phenomenon. However, PCR positivity and temporal association do not establish causality, and a coincidental association cannot be excluded.

Also, this patient had coexistence of CAD. CAD is characterised by cold-reactive IgM antibodies that activate the classical complement pathway, leading to complement-mediated haemolysis [17]. CAD is broadly classified as primary, arising from an underlying clonal B-cell disorder, or secondary, occurring in the context of infection or systemic autoimmune disease. The hallmark laboratory finding is a DAT positive for C3d with absent IgG, reflecting complement deposition rather than direct antibody coating of red cells, a pattern seen in our patient [17].

Infection-associated CAD is most described in the context of *M. pneumoniae* [18], while reports involving *Chlamydia* species are limited and largely limited to *Chlamydia psittaci* [19].

The coexistence of MPO-ANCA vasculitis and CAD has been reported previously only in a single case without an identifiable trigger [20]. Our case adds a distinctive feature to the limited literature by describing this combination in the setting of PCR-detected *C. pneumoniae*, alongside documented MPO-ANCA seropositivity approximately 10 years before the onset of clinical disease. We postulate that *C. pneumoniae* infection may have activated two immunological pathways: a neutrophil-driven process leading to AAV, and a B-cell-mediated process resulting in CAD.

## Conclusions

This case describes the coexistence of MPO-ANCA-associated crescentic GN and CAD in a patient with longstanding asymptomatic MPO-ANCA seropositivity and a recent respiratory illness with *C. pneumoniae* detected by PCR. The temporal relationship raises the possibility of an infection-associated second-hit phenomenon, although causality cannot be established. The case highlights that MPO-ANCA seropositivity may precede clinical vasculitis for many years and that concurrent haematological abnormalities warrant appropriate evaluation for cold agglutinin-mediated haemolysis.

## Additional Information

### Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

**Concept and design:** Hassan Abdelwahab

**Acquisition, analysis, or interpretation of data:** Hassan Abdelwahab, Rebecca Brown, Hannah Sammut, Innocent Segamwenge, Mohamed Ahmed

**Drafting of the manuscript:** Hassan Abdelwahab, Innocent Segamwenge

**Critical review of the manuscript for important intellectual content:** Hassan Abdelwahab, Rebecca Brown, Hannah Sammut, Innocent Segamwenge, Mohamed Ahmed

**Supervision:** Rebecca Brown

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