

# Macrolide Therapy and Alveolar Hemorrhage Secondary to Granulomatosis with Polyangiitis

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## Abstract

We report the case of a 64-year-old woman with severe alveolar haemorrhage secondary to granulomatosis with polyangiitis (GPA), who was unknowingly treated with only penicillin and macrolide antibiotics, resulting in successful initial disease remission. The immunomodulatory effects of the macrolide antibiotic used could underlie this novel observation, which may shed new light on the pathogenesis and potential treatment of anti-neutrophil cytoplasm antibody (ANCA) associated vasculitis. The role of macrolides as an adjunct to conventional therapy in cases of AAV with respiratory involvement may be worthy of further investigation.

**Keywords:** Vasculitis; Anti-bacterial agents; Lung disease; Renal disease

## Introduction

Alveolar haemorrhage is one of the most serious manifestations of GPA, which can be rapidly fatal if untreated. Standard immunosuppressive treatment for GPA carries significant toxicity, and on-going research seeks better-tolerated, efficacious regimens. We present a case whose clinical course may be informative with regards pathogenesis and management of AAV.

## Case Report

A 64-year-old woman presented with a four-week history of haemoptysis, fever and malaise. She had no previous medical history, aside from high-frequency hearing loss for several years. Examination revealed temperature of 38.3°C, bronchial breathing at the right lung base, and hypoxia (PaO<sub>2</sub> 8.5 kPa on room air).

Laboratory studies demonstrated anaemia (haemoglobin 64 g/L), leucocytosis (13.9 × 10<sup>3</sup> cells/μL), normal renal function (creatinine 76 μmol/L), and elevated C-reactive protein (456 mg/L; NR < 10 mg/L). Chest x-ray revealed extensive consolidation affecting the right middle and upper lobes (Figure 1A). Fiberoptic bronchoscopy found purulent secretions and fresh blood in the right lung. Culture of sputum and broncho-alveolar lavage yielded no bacterial organisms, and staining for acid-fast bacilli was negative.

Treatment with intravenous piperacillin-tazobactam and clarithromycin was commenced, and two units of red cells were transfused. She received no inhaled, oral or intravenous corticosteroids. Her condition improved rapidly, and she was discharged after eight days. A repeat chest x-ray at follow-up two months later showed complete resolution of the abnormalities (Figure 1B).

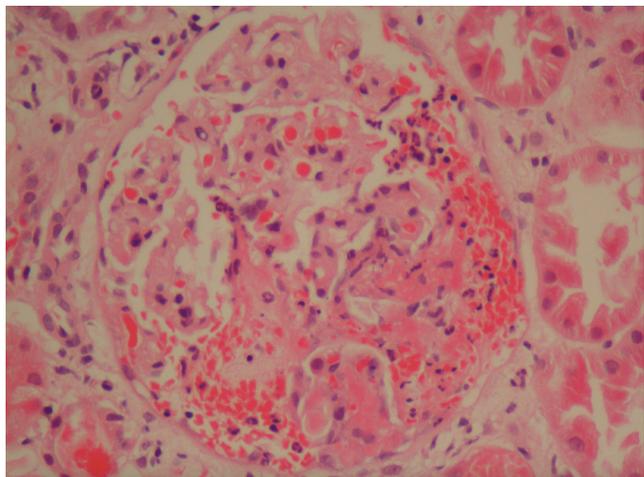


**Figure 1:** a) Chest radiograph at presentation demonstrating significant airspace shadowing in the right middle and upper lobes. b) Chest radiograph after two months and following antibiotic treatment showing complete resolution of the previous findings.

On retrospective review, serum taken at presentation demonstrated positive immunofluorescence staining for ANCA in a cytoplasmic pattern, with antibodies to proteinase-3 (PR3) at a titre of 143 IU/mL (NR < 3 IU/ml). Anti-glomerular basement membrane antibodies were negative. Urine analysis detected microscopic haematuria (3+ red blood cells on dipstick), and no proteinuria. Culture of nasal swabs yielded no organisms.

For ten months after her initial presentation, the patient remained entirely well, with normal blood pressure and renal function, and no respiratory symptoms. Microscopic haematuria persisted, and her PR3-ANCA titre remained elevated (120 IU/mL). She then developed haemoptysis and malaise, acute kidney injury (creatinine 188 μmol/L), anaemia (haemoglobin 88 g/L) and an increase in PR3-ANCA titre (143 IU/mL). Chest x-ray revealed consolidation in the left lower zone, and her carbon monoxide transfer factor was elevated (110%). A renal biopsy (Figure 2) showed pauci-immune focal segmental necrotizing

crescentic glomerulonephritis. She was treated with intravenous glucocorticoids, cyclophosphamide and rituximab, which resulted in a rapid clinical response. Her disease has since followed a relapsing course, and she is now receiving regular rituximab to maintain remission.



**Figure 2:** Photomicrograph of section of renal biopsy, showing focal segmental necrotizing crescentic glomerulonephritis (Haematoxylin and Eosin, x40 magnification).

## Discussion

The initial presentation of the case described is clearly consistent with a diagnosis of severe alveolar haemorrhage secondary to pulmonary GPA, and had the ANCA result been available early on during the course of her disease, she would undoubtedly have received immunosuppressive treatment for ANCA associated vasculitis with pulmonary haemorrhage. However, due to the delay in reaching this diagnosis, standard immunosuppressive treatment was not administered. Interestingly, following treatment with only beta-lactam and macrolide antibiotics she had complete resolution of disease, and remained well for ten months. We are unaware of any similar observations in the published literature. This observation could be explained in two different ways: first, that pulmonary vasculitis was provoked by an unidentified bacterial pathogen, the eradication of which eliminated the stimulus for persistent autoimmune damage; second, that the disease was not provoked by infection and remission resulted from an immunomodulatory effect of the antibiotics used. Below, we discuss the evidence for each of these theories.

Bacterial infection is widely considered as a potential trigger of GPA, a theory which was advanced when the disease was first described. Mechanisms through which infection may result in a loss of tolerance and induction of autoimmunity include neutrophil “priming” by inflammatory cytokines, molecular mimicry of self- and pathogen-derived peptides, stimulation of auto-reactive lymphocytes by bacterial super-antigen, and modulation of toll-like receptor (TLR) signalling [1]. Clinically, nasal and bronchial carriage of *Staphylococcus aureus* are associated with disease activity [2,3] and there are also reports of AAV in association with other bacterial [4] and viral [5] infections. In terms of antimicrobial therapy, it has been shown that eradication of nasal *S. aureus* reduces the rate of relapse [6], however, the role of

adjunctive antibiotics in induction therapy is unproven, beyond pneumocystis prophylaxis with cyclophosphamide. The only trial directly examining this question found that benefit from co-trimoxazole was limited to patients with disease confined to the respiratory tract, and no constitutional symptoms; notably, one third of the patients in this study had previously received immunosuppression [7]. To our knowledge there are no reports of AAV in any organ system responding to treatment with beta-lactam or macrolide antibiotics.

Macrolide antibiotics share a common structure based around a macrocyclic lactone ring. As well as being effective against many gram-positive and some gram-negative bacteria, their immunomodulatory properties are well-described [8]. Various agents from this class of drug are used in the treatment of chronic inflammatory respiratory diseases [9], with anti-inflammatory effects that are likely independent of their antimicrobial action [10]. Experimental and clinical studies show that macrolides cause increased leucocyte apoptosis, reduced cytokine expression, and impaired T-cell proliferation and signalling [11]. Administration of oral clarithromycin to patients with bronchiectasis has been shown to cause local and systemic modulation of the Th17 axis [12], which has also been implicated in the pathogenesis of AAV [13]. Tacrolimus and rapamycin (sirolimus) are non-antimicrobial macrolides widely used in transplantation medicine. Though there is no evidence for the use of these agents in AAV, recent trials support the use of tacrolimus as an adjunct in the treatment of lupus nephritis [14]. Experimental evidence also suggests a role for rapamycin in the treatment of rapidly progressive glomerulonephritis [15]. We have found no published reports on the use of traditional (antimicrobial) macrolides in experimental or clinical vasculitis.

It is certainly possible that the response observed in our patient was due to the eradication of a bacterial stimulus. However, it is perhaps unusual to culture no organisms in such a severe case of pneumonia. In addition, the antecedent history of hearing loss and sub-acute onset of symptoms suggest that a vasculitic process was already established. Ultimately, it is impossible to prove which of the two theories outlined above is correct, and it may have been a combination of the two factors; however, our case is unusual and striking, and potentially supports the immunomodulatory properties of macrolide antibiotics. We believe that other physicians may have noticed similar clinical patterns but not reported them. A more widespread finding could support a formal study of adjunctive macrolide therapy in AAV induction therapy.

In summary, we present a case of relapsing GPA, initially manifesting with severe alveolar haemorrhage, in whom prolonged remission was unknowingly achieved with antibiotic therapy alone. The immunomodulatory effect of clarithromycin is likely to have contributed to this clinical finding. Whilst we of course do not advocate using macrolide antibiotics alone for the treatment of GPA, their adjunctive use may be worthy of further investigation.

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