Case Report

A case of phenotypic and serological transformation in Wegener’s granulomatosis

Frank Ward¹, David Brophy² and Alan Watson¹

¹Department of Nephrology and ²Department of Radiology, St. Vincent’s University Hospital, Dublin, Ireland

Abstract
Wegener’s granulomatosis (WG) is a systemic vasculitis of small- to medium-sized arteries, associated with necrotizing granulomata classically involving the upper and lower respiratory tracts and kidneys. It is usually associated with the presence of anti-neutrophil cytoplasmic antibodies (ANCA). ANCA-negative WG is usually a limited form of the disease that tends to affect organs other than the kidneys, often the central nervous system. We describe an unusual case presenting with ANCA-positive WG affecting the kidneys and upper airway that, despite standard treatment, demonstrated a phenotypic and serological transformation into an aggressive ANCA-negative WG affecting the central nervous system.

Keywords: ANCA negative; central nervous system; Wegener’s granulomatosis

Introduction
Wegener’s granulomatosis (WG) was first described in a report in 1936 [1]. The aetiology of this condition remains poorly understood. Since the early 1980s, diagnosis has been aided by the presence of anti-neutrophil cytoplasmic antibodies (ANCA) on immunofluorescence, typically in a cytoplasmic pattern in WG, and more recently the ability to detect specific antibodies to proteinase-3 (PR3). Cases of ANCA-negative WG have been well described and are particularly linked to cerebral manifestations [2] and other limited forms of the disease [3,4]. There is ongoing debate regarding a direct pathogenic role of ANCA in the condition, but there is a mounting evidence base in its favour.

Case report
An 18-year-old male with no significant medical history presented in January 2006 with a 5-day history of painless haematuria, knee pain and a red eye. This was preceded by a 2-month prodrome of fatigue, arthralgia and intermittent epistaxis. Physical examination revealed normotension, euvoilaemia and bilateral corneal injection. Urinalysis showed an active sediment, and blood tests showed a serum creatinine of 771 μmol/L, giving an MDRD-eGFR of 8.5 mL/min/1.73 m². ESR titre was 105 mm/h. Cytoplasmic ANCA (c-ANCA) was positive with an immunofluorescence titre of >1:1280, and anti-PR3 antibody was positive by ELISA; no antibody titre was available. Haemodialysis was commenced, and a renal biopsy demonstrated extensive active cellular crescent formation with segmental necrotizing inflammation (Figure 1). A diagnosis of systemic WG was made, and oral cyclophosphamide 100 mg daily, with high-dose oral glucocorticoids, was commenced. The patient improved significantly and was discharged on maintenance haemodialysis. ANCA titre at discharge had fallen to 1:320.

Fourteen days later, the patient was readmitted following generalized seizures. A computed tomography (CT) scan of the brain showed no abnormality, nor did EEG. An MRI of the brain showed several non-specific focal areas of high signal in the sub-cortical white matter of the left frontal lobe and both parietal lobes. Repeat c-ANCA titre remained at 1:320, with anti-PR3 antibody titre of 24 U/mL (normal 0–7 U/mL). A formal cerebral angiogram was normal. The patient made a good recovery and was maintained on oral phenytoin without further seizures. Cerebral vasculitis was felt to be unlikely given stable ANCA titres and ongoing treatment with cyclophosphamide and steroids. One month later, the patient presented emergently following a generalized tonic–clonic seizure, while still taking the same induction therapy. A repeat MRI scan showed no interval changes, and a repeat EEG was non-diagnostic. c-ANCA titre had fallen to 1:160, with anti-PR3 antibody titre of 18 U/mL. The patient’s condition stabilized on antiepileptic drugs, and at discharge 6 weeks later, the c-ANCA titre had fallen to 1:20. Cyclophosphamide had been switched to azathioprine as 3 months therapy had been completed. The patient was monitored closely and had multiple negative ANCA tests over the next 11 weeks.

In June 2006, the patient suffered refractory seizures post-dialysis. Serology revealed a negative ANCA test. Possible triggers for the seizures were thought to be low serum phenytoin levels post-dialysis, occult infection.
or electrolyte disturbance. Neutrophil count was low at 1700/mm³, and azathioprine was held. An MRI scan showed significant progression of changes as compared with March 2006. The patient was switched to mycophenolate mofetil (MMF) 250 mg twice daily and high-dose oral prednisolone to cover the possibility of vasculitis. One week later, the patient developed a seizure in the setting of a line-related staphylococcal neutropaenic bacteremia. MMF was held, and the patient received GCSF. ANCA was again negative. Cerebrospinal fluid analysis excluded CNS infection. Repeat MRI showed diffuse white matter changes (Figure 2A). Serial MRI images were reviewed, and in the absence of infection. Although there was no dural enhancement, the overall picture suggested cerebral vasculitis associated with Wegener’s granulomatosis. The patient was treated with pulsed methylprednisolone on three consecutive days with reintroduction of MMF at 500 mg twice daily. However, the patient soon after deteriorated acutely with seizures. ANCA remained negative. An MRI showed more extensive lesions, likely to be vasculitic ischaemia (Figure 2B). Pulsed intravenous cyclophosphamide was commenced, with high-dose oral prednisolone. MMF 500 mg twice daily was also continued. Within 5 days, a repeat MRI had a significantly improved appearance (Figure 2C), and the patient had no further generalized seizures.

Subsequently, the patient had a number of admissions with neutropaenic sepsis, and cyclophosphamide was discontinued after four doses. The patient was maintained on gradually reducing oral prednisolone alone. Serial MRI scans showed continuing improvement, and a scan in January 2007 was essentially normal (Figure 2D). The patient was later transferred onto peritoneal dialysis, and in June 2008, he underwent an uneventful cadaveric renal transplant and is maintained on MMF, tacrolimus and prednisolone. Currently, the patient is clinically well and seizure-free since August 2006.

Discussion

This case draws attention to an unreported phenomenon involving a phenotypic and serological transformation of classical ANCA-positive WG to an ANCA-negative cerebral vasculitis despite standard treatment over a relatively short period. The patient presented with predominantly renal and upper airway involvement of WG and thereafter developed a central nervous system disorder in the setting of appropriate treatment, declining ANCA titres with subsequent ANCA negativity, a normal cerebral angiogram and later MRI changes consistent with vasculitis. This disorder was refractory to MMF and pulsed intravenous glucocorticoids but demonstrated a rapid clinical and radiological resolution following the use of pulsed intraven-
ous cyclophosphamide, which confirmed the clinical diagnosis of cerebral vasculitis secondary to ANCA-negative WG.

ANCA is positive in >90% of WG cases [5], and 65–70% of limited WG cases [6,7]. Central nervous system involvement is reported in up to 50% of WG cases and includes cranial nerve palsies, seizures, cerebrovascular accidents and peripheral neuropathy. ANCA-associated vasculitis relapses are reported to occur most likely in the same organ as initial presentation [8]. There are also reports of ANCA-positive WG relapsing within the same organ as ANCA-negative [9]. The case reported here is unusual owing to the dramatic phenotypical shift that was displayed in the presence of a reducing ANCA titre and eventual negative ANCA test. It should be noted that the use of serial ANCA measurements for monitoring disease activity in cases of WG remains unproven [10], although it is still often used in clinical practice.

The role of ANCA in the pathogenesis of WG is an area of considerable ongoing research. Clinical observational studies, in vitro studies and in vivo mouse studies have suggested a likely pathogenic role of ANCA in small vessel vasculitis, particularly in the perinuclear ANCA subtype with antibodies to myeloperoxidase [11]. However, experimental rodent models for anti-PR3 ANCA induction of systemic vasculitis have not demonstrated a clear pathogenic role [12]. Our case and other cases of biopsy-proven ANCA-negative WG mitigate against a direct pathogenic role of ANCA in WG.

In conclusion, this report aims to expand the clinical spectrum of WG and highlights the limitation of ANCA assays in the diagnosis and monitoring of relapsing WG.

Conflict of interest statement. None declared.

References

8. Chen M, Yu F, Zhao MH. Relapses in patients with antineutrophil cytoplasmic autoantibody-associated vasculitis: likely to begin with the same organ as initial onset. J Rheumatol 2008; 35: 448–450
12. Pfister H et al. Antineutrophil cytoplasmic autoantibodies against the murine homolog of proteinase 3 (Wegener autoantigen) are pathogenic in vivo. Blood 2004; 104: 1411–1418

Conflict of interest statement. None declared.