

Short reports

Wegener's granulomatosis presenting as acute suppurative interstitial nephritis

A Banerjee, W McKane, S Thiru, K Farrington

Abstract

A 78 year old man presented with acute renal failure following a prolonged respiratory illness. A renal biopsy demonstrated severe suppurative interstitial nephritis with normal glomeruli. After nine weeks of antibiotics he remained anuric and a second biopsy demonstrated pauci-immune, necrotising glomerulonephritis. His subsequent clinical course was consistent with a diagnosis of Wegener's granulomatosis and antineutrophil cytoplasmic antibodies (ANCA) were detected. This is the first reported case of Wegener's granulomatosis presenting with an isolated tubulointerstitial lesion.

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Antineutrophil cytoplasmic antibody (ANCA) associated vasculitis (AAV) involving the kidney usually comprises a pauci-immune, necrotising glomerulonephritis with crescents.¹ We describe a case of AAV that presented with rapidly progressive renal failure; unusually, the initial histopathological features were of an interstitial process suggesting acute pyelonephritis. Although a mononuclear tubulointerstitial infiltrate is a feature of AAV,¹ interstitial inflammation without glomerular disease has not been described. We discuss this case in the light of published data concerning the pathogenesis of AAV, with particular reference to the role of the neutrophil and pyogenic infection.

Case report

A 78 year old man was admitted with a five week history of lethargy, cough, and breathlessness, unresponsive to a prolonged course of co-amoxycylav. He had a two year history of a non-erosive inflammatory arthropathy (rheumatoid factor positive) for which he was taking sulphasalazine and diclofenac. On admission he was systemically unwell but normotensive. A chest x ray showed patchy consolidation at the left base with bilateral pleural effusions. Serum creatinine was 1499 $\mu\text{mol/litre}$ with blood 2+ and leucocytes 2+ on urine microscopy. He was treated with intravenous amoxicillin and ciprofloxacin and commenced on haemodialysis. An ultrasound showed normal sized non-hydronephrotic kidneys.

Examination of all levels of a serially sectioned renal biopsy (fig 1) demonstrated approximately 20 unremarkable cortical glomeruli. There was pronounced interstitial oedema, more severe in the medulla. Prominent aggregates of neutrophils were present both within the lumina of many of the medullary tubules and also the surrounding interstitium. Inflammation was present as streaks through the medulla only. Focal capillaries in these areas showed endothelial cell damage with extravasation of red blood cells. A diagnosis of severe acute pyelonephritis was made, although repeated cultures of urine and blood were negative. Serum ANCA by radioimmunoassay were borderline positive at 13% (0-10), but an immunofluorescence assay was negative. His antinuclear factor was positive (1/320)

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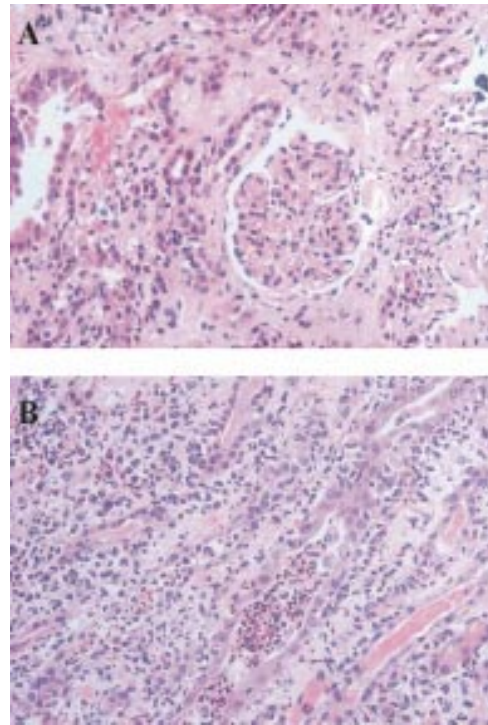


Figure 1 First renal biopsy, (A) cortex and (B) medulla. (A) The glomerulus is essentially unremarkable. The surrounding interstitium is oedematous and has a chronic inflammatory infiltrate. Using morphological criteria, this comprised plasma cells, macrophages, and lymphocytes. (B) Dense aggregates of neutrophils within the lumina of tubules with the lining epithelium showing foci of degeneration and necrosis. The interstitium is oedematous and contains neutrophils and mononuclear inflammatory cells.

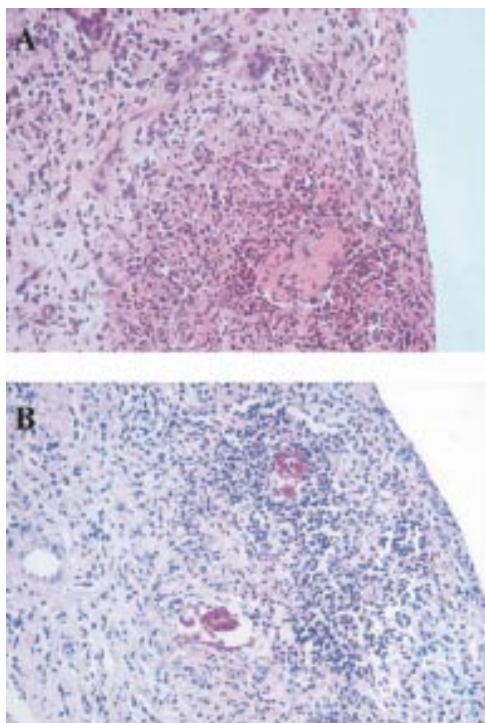


Figure 2 Second renal biopsy, cortex only. (A) Fibrinoid necrosis of glomerulus with an intense acute inflammatory infiltrate giving the appearance of a "micro-abscess". (B) Alcian blue/periodic acid Schiff stain showing two necrotic glomeruli with remnants of glomerular capillary wall within the inflammatory exudate.

but he was normocomplementaemic, with no paraprotein.

He remained febrile and developed a purpuric rash on his ankles. A skin biopsy (day 18) demonstrated a leucocytoclastic vasculitis. A computerised tomogram of the thorax showed confluent bi-basal shadowing with cavitation. A bronchoscopy was normal and cultures of blood, urine, and bronchial washings remained sterile. Changing antibiotics to vancomycin, ceftazidime, and erythromycin did not result in an improvement and he did not respond to empirical anti-tuberculous treatment.

A second renal biopsy (day 64) demonstrated dramatically different morphology, with evidence of an acute necrotising glomerulonephritis with 10% crescents (fig 2). Many of the necrotic glomeruli had the appearance of micro-abscesses with intense neutrophil infiltration. Tubular atrophy and interstitial fibrosis with an infiltrate of mononuclear inflammatory cells was also evident. There was no evidence of an active or healed arteritis, or immune deposits. A diagnosis of pauci-immune, necrotising glomerulonephritis, compatible with Wegener's granulomatosis (WG) or microscopic polyangiitis was made. He was treated with prednisone and cyclophosphamide, and although his general condition improved he remained anuric.

Over the ensuing eight years he has had intermittent relapses of his pulmonary vasculitis (cytoplasmic ANCA positive; enzyme linked immunosorbent assay specificity: bactericidal/permeability increasing protein),² requiring further cyclophosphamide followed by azathioprine. Intercurrent respiratory infections have

been successfully treated with co-amoxiclav or ciprofloxacin. He is currently well, requiring maintenance haemodialysis and prednisone, 7.5 mg daily.

Discussion

Mononuclear tubulointerstitial infiltrates are common in AAV,¹ but these have always been described in conjunction with glomerulitis. The histology of the first biopsy suggested severe pyelonephritis; however, no evidence of urinary tract infection or bacteraemia was demonstrated and antibiotics did not help. He subsequently developed a pauci-immune, necrotising glomerulonephritis and neutrophilic aggregates were now present within the glomeruli. These lesions were distinct from the periglomerular pseudogranulomata previously described in WG, which are composed of macrophages and fibroblasts.¹ The initial ANCA result was equivocal but refinements in laboratory technique later confirmed the presence of cytoplasmic ANCA. The subsequent clinical course, with prominent respiratory involvement, was consistent with a diagnosis of WG, although no respiratory granulomata were demonstrated by histology. The unusual features of our case pose a series of interesting questions relevant to the pathogenesis of AAV.

Neutrophils are key immune cells participating in early events in AAV.³ Intravascular activated neutrophils are found at sites of endothelial injury in humans with WG and in animal models of vasculitis.⁴ The specialised endothelia of glomerular and pulmonary capillaries appear to be particularly prone to neutrophil driven injury. ANCA may amplify this process, activating neutrophils expressing appropriate autoantigens on their cell surface by means of co-ligation of Fc γ receptors. This is thought to stimulate a respiratory burst and influence cell trafficking, with intravascular retention of neutrophils at sites of endothelial activation.³ Cell membrane proteinase 3 positive neutrophils are detected in both AAV and rheumatoid arthritis,⁵ although this patient's non-erosive arthropathy may have been an early manifestation of vasculitis, rather than rheumatoid disease. Hence, the presence of neutrophils in the first biopsy is not surprising. The feature inconsistent with current understanding of the pathogenesis of AAV is the location of the neutrophils, which were not in the glomerular capillaries, but in the tubulointerstitium.

Micro-abscess formation has been described in WG, although not in the kidney. In a review of pulmonary WG, extravascular lesions including interstitial pneumonitis and micro-abscesses were seen in 12 of 20 patients.⁶ It is possible that the corresponding tubulointerstitial changes in the first biopsy may have represented early events in the evolution of this patient's vasculitis.

The only previous report of systemic vasculitis associated with pyelonephritis describes Henoch Schonlein purpura.⁷ Chronic pulmonary infection is associated with WG, nasal staphylococcal infection is a risk for relapse, and co-trimoxazole is used as prophylaxis for

patients in remission.⁸ This relation between pyogenic infection and vasculitis may pertain to the breakdown of immunological tolerance that produces ANCA. Cryptic neutrophil cytoplasmic antigens are translocated to the cell surface after cytokine priming. In vasculitis, bacterial infections may provide the proinflammatory stimulus for priming and initial endothelial cell activation.³ Once present, ANCA may amplify the vasculitic process by converting a local inflammatory reaction to a systemic vasculitis. Hence, the detection of ANCA is an almost universal finding in systemic WG, but they are detected in only 50% of patients with disease limited to the upper respiratory tract.³

This patient had a leucocytoclastic cutaneous vasculitis consistent with the diagnosis of a drug reaction; however, the renal histology was not typical of a drug induced lesion. Systemic vasculitis can follow drug treatment, but the agents usually implicated are hydralazine, propylthiouracil, and D-penicillamine,⁹ and not the antibiotics that this patient had received. Furthermore, subsequent use of the same antibiotics did not produce a relapse of his vasculitis. Cutaneous vasculitis has been described after alclofenac treatment¹⁰; however, our patient's skin lesion occurred almost three weeks after stopping diclofenac.

Our current understanding of the pathogenesis of AAV leads us to believe that the suppurative interstitial nephritis seen in the first biopsy represented an early event in the natural history of our patient's vasculitis. Whether this

was the vasculitis itself, or a transition from infection to vasculitis associated with ANCA formation, cannot be established. It is probable that there was some infectious trigger, but previously published data suggest that this was more likely to have been a respiratory infection than pyelonephritis. Physicians should be aware of this rare presentation of WG, because early diagnosis may allow recovery of renal function.

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