Rare disease

Life-threatening ANCA-positive vasculitis associated with rickettsial infection

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Summary

We present a 47-year-old Caucasian fire fighter who developed multisystem organ failure in the setting of a positive antineutrophil cytoplasmic autoantibody (myeloperoxidase) as well as confirmed Rocky Mountain spotted fever by skin biopsy PCR. This case provided a diagnostic challenge, a rare association of a *Rickettsia* infection and autoimmune vasculitis as well as a unique management approach.

BACKGROUND

The antineutrophil cytoplasmic autoantibody (ANCA)-associated vasculitides comprise a group of clinical syndromes that include Wegner's granulomatosis, microscopic polyangiitis and Churg-Strauss syndrome.^{1 2} The defining characteristic of each is a necrotising inflammation of small vessels, which exists in the presence of a positive ANCA directed at either proteinase 3 (PR3) or myeloperoxidase (MPO). Until recently, the pathogenic nature of ANCA itself remained extremely controversial. Experimental studies, however, have provided evidence that these antibodies directly activate neutrophils and cause pauci-immune glomerular necrosis.^{3 4} Certain types of vasculitis have been linked to specific infections such as polyarteritis nodosa and hepatitis B virus. Recently, pre-existent infections, particularly with *Staphylococci*, have been implicated in the pathogenesis of Wegener's granulomatosis. We present a 47-year-old Caucasian fire fighter who developed multisystem organ failure in the setting of a positive ANCA (MPO) as well as confirmed Rocky Mountain spotted fever by skin biopsy PCR. This case provided a diagnostic challenge, a rare association of a *Rickettsia* infection and autoimmune vasculitis as well as a unique management approach.

CASE PRESENTATION

While on vacation in the Outer Banks, North Carolina, the patient presented to the local emergency department (ED) with severe fatigue, nausea and worsening diarrhoea. He had a medical history of hypertension, hyperlipidaemia and asthma. Two months before presentation he developed fatigue and swelling (lymphadenopathy) first in his neck and then in his axilla, for which he received two courses of antibiotics. After the second course of antibiotics he developed non-bloody diarrhoea. He was seen in the ED and was started empirically on ciprofloxacin, which was changed 2 days later to metronidazole following a positive assay for *Clostridium difficile* toxin. He represented to the emergency room a few days later with decreased urine output and severe abdominal pain. Physical examination was remarkable for a petechial rash on the heels and soles of his feet. He was febrile to 39°C

and hypotensive with a blood pressure of 85/60 mm Hg. He was resuscitated with fluids and started on a broad spectrum of antibiotics including doxycycline. The patient was then transferred to our intensive care unit (ICU) where over the next 24 h he developed progressive multisystem organ failure requiring mechanical ventilation, maximal vasopressor support and continuous renal replacement therapy. The rash spread across his upper extremities and trunk and coalesced to form purpura of the lower extremities. He then developed necrosis of his distal extremities. The CT scan revealed axillary, hilar, mediastinal, abdominal, and retroperitoneal adenopathy, scattered pulmonary nodules, bilateral lower lobe consolidation, small pleural effusions, hepatosplenomegaly, enlarged kidneys with perinephric stranding as well as pelvic and retroperitoneal ascites. Owing to concern over toxic megacolon he underwent exploratory laparoscopy which showed evidence for only mild pseudomembranous colitis.

INVESTIGATIONS

Given the widespread adenopathy and concern over an underlying lymphoproliferative disease, he underwent axillary node and bone marrow biopsy. The biopsies that were reviewed by the National Institute of Health/National Cancer Institute were reported to be 'most consistent with a severe reactive process.' A subsequent skin biopsy demonstrated a leucoclastic vasculitis (see figure 1). Infectious work-up was negative including all blood and tissue cultures, HIV and serology for hepatitis B and C, Rocky Mountain spotted fever, *Anaplasma phagocytophilum*, ehrlichiosis, brucellosis and leptospirosis. Given the patient's continued clinical decline and negative infectious work-up, he was started empirically on high-dose hydrocortisone, which was given by continuous infusion (50 mg/h; 1200 mg/day). Autoimmune work-up revealed a positive P-ANCA (1:80) and MPO antibody (26.2 µ/ml). Within hours of the initiation of the steroid infusion his clinical status improved. Since the diagnosis was unclear, he was continued on a full course of doxycycline and the steroid infusion was continued for 7 days and then slowly

Figure 1 Skin biopsy demonstrating superficial dermal capillaries with perivascular inflammation, including neutrophils and 'nuclear dust' consistent with a leucocytoclastic vasculitis.

tapered to a maintenance dose of prednisone 40 mg daily. The presumptive diagnosis of ANCA-positive vasculitis (Churg-Struass syndrome vs microscopic polyangiitis) was made. However, a week later the PCR from the skin biopsy was strongly positive for *Rickettsia rickettsii* (Rocky Mountain spotted fever). The patient made a full recovery with the exception of the loss of the phalanges on three fingers.

TREATMENT

Given the patient's continued clinical decline and negative infectious work-up, he was started empirically on high-dose hydrocortisone, which was given by continuous infusion (50 mg/h; 1200 mg/day). Autoimmune work-up revealed a positive P-ANCA (1:80) and MPO antibody (26.2 µ/ml). Within hours of the initiation of the steroid infusion, his clinical status improved. Since the diagnosis was unclear, he was continued on a full course of doxycycline and the steroid infusion was continued for 7 days and then tapered over a period of 7 days to a maintenance dose of prednisone 40 mg daily. The presumptive diagnosis of ANCA-positive vasculitis (Churg-Struass syndrome vs microscopic polyangiitis) was made. However, a week later the PCR from the skin biopsy was strongly positive for *R. rickettsii* (Rocky Mountain spotted fever).

OUTCOME AND FOLLOW-UP

The patient made a full recovery with the exception of the loss of the phalanges on three fingers. Although the patient initially received high-dose steroids, he did not develop any obvious steroid-related side effects. He was discharged home on prednisone 20 mg/day to follow up with his primary care provider and a rheumatologist (who remained in contact with us). The patient visited the ICU 3 months later; he was able to ambulate unassisted and appeared to be in good health.

DISCUSSION

Antineutrophil cytoplasmic autoantibodies are directed against proteins contained in the lysosomal compartments of neutrophils and monocytes.^{1 2} Although the presence

of these antibodies (against either PR3 or MPO) is strongly associated with the development of Wegner's granulomatosis, microscopic polyangiitis and Churg-Struass syndrome, their exact role has been controversial. However, recent studies suggest that these antibodies play a role in the pathogenesis of ANCA-associated vasculitis via the activation of neutrophils, cytokine release and the generation of superoxide radicals. The relationship between infection, most notably hepatitis C, and vasculitis has been well established. Stageman *et al*⁵ first demonstrated the link between Wegner's granulomatosis and *Staphylococcus aureus* by demonstrating that up to 70% of those diagnosed with Wegner's granulomatosis are chronic carriers of this bacterium. Subsequently, anti-MPO-ANCA-positive vasculitis was reported following *S. aureus* endocarditis.^{6 7} Tadema *et al*⁸ demonstrated that cytosine-phosphate-guanine oligodeoxynucleotide (CpG-ODN) motifs from staphylococcal DNA could trigger ANCA production in vitro in patients with ANCA-associated vasculitis in remission. Interestingly, antibacterial treatment with co-trimoxazole reduces the risk of relapse in patients with Wegner's granulomatosis as part of maintenance therapy.⁹ These findings point towards a link between infection and autoimmunity; however, the underlying mechanisms are unknown and only a few specific infections have been consistently implicated.¹⁰

When transmitted to a human host, pathogenic *R. rickettsii* (Rocky Mountain spotted fever) localise and multiply in the endothelial cells of small-to-medium-sized blood vessels.¹¹ The major pathophysiological effect of rickettsial infection is increased vascular permeability caused by disruption of cell adhesion between infected endothelial cells. Endothelial cell injury is followed by immune and phagocytic cellular responses via local accumulation of lymphocytes and macrophages, resulting in a lymphohistiocytic vasculitis.¹² We believe our case is the first description of an ANCA-positive leucocytoclastic vasculitis in a patient with confirmed *R. rickettsii* infection. As hypothesised by previous authors we suggest a 'two hit' model to explain our patient's severe multisystem disease. The presence on an ANCA antibody acted as a primer for the development of full-blown vasculitis after the exposure to the infectious agent (*R. rickettsii*). This model is supported by observations of infectious episodes before or at diagnosis of ANCA-associated vasculitis and by in vitro studies that have shown that ANCAs are capable of activating neutrophils and monocytes primed with inflammatory cytokines.

It is worth noting that we treated our patient with a high dose of hydrocortisone (equivalent to 240 mg methylprednisolone/day or 2.4 mg/kg/day) given as a continuous infusion for 7 days. The usual dose of methylprednisolone for the treatment of vasculitis is 1 mg/kg/day; however, pulse dosing of 1 g methylprednisolone for 3 days has been used in patients with life-threatening vasculitis.¹³ We chose this dosing regimen due to the life-threatening nature of the patient's disease, and hypothesised that a continuous infusion would result in a sustained and less fluctuating immunosuppressive effect. A number of studies have demonstrated better glycaemic control (fewer glucose fluctuations) when patients receive glucocorticoids as a continuous infusion.^{14 15} A recent randomised controlled trial in trauma patients demonstrated a lower incidence of hospital acquired pneumonia and

improved outcomes in patients randomised to a continuous steroid infusion (200 mg hydrocortisone/day for 5 days followed by a taper).¹⁶ It is, however, unclear if the novel glucocorticoid dosing regimen that we used played a role in our patient's recovery.

In conclusion, we would like to highlight the rare association of rickettsial infection with an ANCA-positive vasculitis. Furthermore, a continuous 'high' dose glucocorticoid infusion may have a role in patients with severe small vessel vasculitis.

Learning points

- ▶ A small vessel vasculitis should be considered in patients developing unexplained multisystem organ failure.
- ▶ A precipitating infectious aetiology should be excluded in patients who present with an antineutrophil cytoplasmic autoantibody positive vasculitis.
- ▶ A continuous glucocorticoid infusion may hold promise for the treatment of patients with life-threatening vasculitides.

Competing interests None.

Patient consent Obtained.

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