Occult microscopic polyangiitis presenting as pyrexia of unknown origin

Introduction

Microscopic polyangiitis is a multisystem small vessel necrotizing vasculitis, classically associated with perinuclear anti-neutrophil cytoplasmic antibodies, which target myeloperoxidase as their antigen. Anti-neutrophil cytoplasmic antibody-positive renal vasculitis is the most common cause of rapidly progressive (crescentic) glomerulonephritis. Its life-threatening natural course may be modified substantially by current treatment modalities.

Pyrexia of unknown origin has previously been described as a presenting feature of microscopic polyangiitis, but in all published cases, investigation has revealed multiple end-organ involvement (Akar et al, 2002; Ohnuma et al, 2010). This article reports a case of microscopic polyangiitis, presenting as a 'pyrexia of unknown origin', without clinical evidence of end-organ involvement at presentation.

Discussion

Pyrexia of unknown origin is a common presentation in hospital practice and often causes a diagnostic challenge. Studies suggest that inflammatory conditions account for 33% of cases and infections at around 30% (Efstathiou et al, 2010).

Anti-neutrophil cytoplasmic antibody-positive associated vasculitis may present as a pyrexia of unknown origin, although subsequent investigation frequently highlights multiple organ failure. Cases of myeloperoxidase anti-neutrophil cytoplasmic antibody-positive vasculitis presenting as pyrexia of unknown origin with pulmonary fibrosis and liver dysfunction have been described in the literature (Ohnuma et al, 2010; Shields, 2011).

This case illustrates that a pyrexia of unknown origin can precede renal involve-

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Figure 1. Glomerulus with fibrinoid necrosis (stars) and a cellular crescent. The remaining glomerular tuft does not show proliferation. Jones methenamine silver stain, magnification 400x.

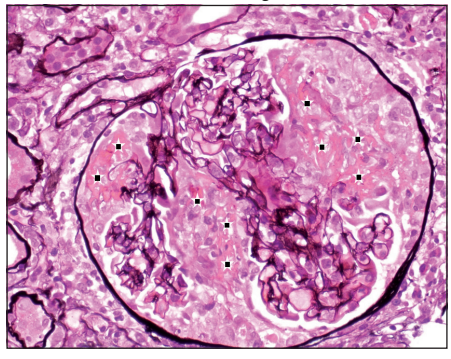
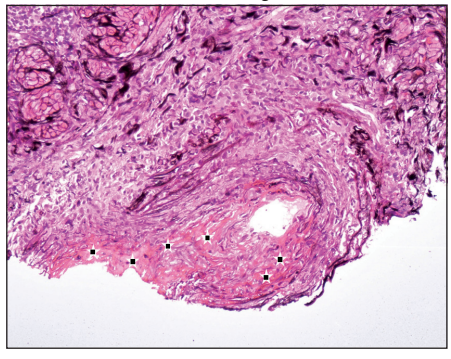


Figure 2. Large artery with transmural inflammation and fibrinoid necrosis (stars). Jones methenamine silver stain, magnification 200x.



Case Report

A 72-year-old man was admitted with a 2-week history of fever, extreme fatigue, rigors, nights sweats and general malaise. Admission bloods showed a normal haemoglobin of 125 g/litre, with a raised white cell count 17.8 x10^9/litre (neutrophils 13.9 x10^9/litre), C-reactive protein of 153 mg/litre and erythrocyte sedimentation rate of 102 mm/hr. Renal and liver function tests were normal, with negative blood and urine cultures. A myeloma screen and tumour markers were negative, as was a tuberculosis Eli spot and malaria screen. Tests for cytomegalovirus, Epstein–Barr virus, hepatitis B and C, and human immunodeficiency virus were negative. Complement levels were also normal.

A chest radiograph, a computed axial tomographic scan of the chest, abdomen and pelvis and an echocardiogram were normal, the latter showing no evidence of endocarditis.

An empirical 10-day course of antibiotics (ciprofloxacin and metronidazole) was prescribed together with 4 days of gentamicin, which failed to settle the pyrexia or reduce inflammatory markers.

Both myeloperoxidase anti-neutrophil cytoplasmic antibody was positive at over 100 Elisa units (normal range 0–10 Elisa units) and double-stranded DNA was positive at over 200 iu/ml (normal range 0–40 iu/ml). Positron emission tomography scanning, while still an inpatient, showed no abnormal uptake of the radio-isotope-labelled glucose analogue 2-deoxy-2-(18F) fluoro-D-glucose. On discharge, renal function was normal and urine dipstick negative.

One month after discharge his fever had resolved with no obvious systemic symptoms of vasculitis. He had lost 7–8 kg in weight and continued to have raised inflammatory markers (C-reactive protein 95 mg/litre, erythrocyte sedimentation rate 105 mm/hr) and a normocytic normochromic anaemia (haemoglobin 86 g/litre). Urine analysis now showed an active sediment with 3+ of blood and 2+ of protein. Serum creatinine had also risen from 103 mmol/litre to 149 mmol/litre since discharge.

A renal biopsy (*Figure 1*) showed a pauci-immune segmental necrotizing glomerulonephritis with crescents, with vasculitis in a large artery (*Figure 2*), substantiating a diagnosis of anti-neutrophil cytoplasmic antibody-positive vasculitis. The patient underwent treatment with two cycles of rituximab and four cycles of cyclophosphamide.

Maintenance therapy comprised azathioprine. The kidney function currently remains stable on follow up, at 3 months.

ment in myeloperoxidase anti-neutrophil cytoplasmic antibody vasculitis. Rapid investigations and treatment are necessary and can substantially modify the course of this condition.

When the natural history of anti-neutrophil cytoplasmic antibody-associated vasculitis was described in 1958, it frequently proved fatal. Without effective treatment, patient survival averages almost 5 months from diagnosis. The introduction of glucocorticosteroids in the 1960s extended average survival by around 8 months. This changed radically when Fauci and Wolff (1973) pioneered the use of cyclophosphamide. Rituximab was later trialled as a first-line induction therapy for anti-neutrophil cytoplasmic antibody vasculitis and showed equivalent efficacy with no excess of adverse effects (Jones et al, 2010). Once disease quiescence is achieved, maintenance therapy is needed to prevent disease relapse.

Untreated, systemic vasculitis is associated with a high mortality rate. Therapies have led to marked improvements in survival of 84% and 76% at 1 and 5 years respectively (Samarkos et al, 2005). Important predictors of death include age, serum creatinine level at presentation, disease extent and severity at diagnosis (Fauci and Wolff, 1973).

Conclusions

The kidney is the most commonly affected vital organ in anti-neutrophil cytoplasmic antibody-associated vasculitis. This case demonstrates a rare cause of pyrexia of unknown origin, with no initial evidence of clinical organ involvement. It highlights the need for close monitoring and follow up of such patients. BJHM

Akar H, Ozbasli-Levi C, Senturk T et al (2002) MPO-ANCA-associated small vessel vasculitis presenting as fever of unknown origin. *Nephron* **92**: 673–5

Efstathiou SP, Pefanis AV, Tsiakou AG et al (2010) Fever of unknown origin: discrimination between infectious and non-infectious causes. *Eur J Intern Med* **21**: 137–43

Fauci AS, Wolff SM (1973) Wegener's granulomatosis: studies in eighteen patients and review of the literature. *Medicine* **52**: 535–61

Jones RB, Tervaert JW, Hauser T et al (2010) Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. *N Engl J Med* **363**(3): 211–20

Ohnuma K, Hosono O, Katayose T et al (2010) Microscopic polyangiitis initiated with liver dysfunction, calf pain and fever of unknown origin. *Rheumatol Int* **30**: 1651–6

Samarkos M, Loizou S, Vaiopoulos G, Davies KD (2005) The clinical spectrum of primary vasculitis. *Sem Arth Rheum* **35**: 95–111

Shields O (2011) Pyrexia of unknown origin and pulmonary fibrosis as a presentation of MPO-ANCA associated vasculitis. *BMJ Case Rep* Apr 15 doi: 10.1136/bcr.01.2011.3692

LEARNING POINTS

- A pyrexia of unknown origin is the result of inflammatory conditions in around a third of cases.
- A pyrexia of unknown origin can proceed clinical evidence of end-organ involvement in myeloperoxidase anti-neutrophil cytoplasmic antibody-related vasculitis.
- Patients with myeloperoxidase anti-neutrophil cytoplasmic antibody-related vasculitis with no apparent end-organ involvement need close monitoring and follow up.

Haematuria: an uncommon presentation of a common vascular diagnosis

A 63-year-old man presented to urology with isolated new onset haematuria. He had sinus tachycardia and no other haemodynamic compromise. His computed tomography scan confirmed an infra-renal abdominal aortic aneurysm with communication to the inferior vena cava causing an aorta-caval fistula (*Figure 1*).

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Abdominal aortic aneurysms can rupture into the retroperitoneum or into the peritoneal cavity; rarely they can rupture into the inferior vena cava. This can present as high output cardiac state and failure. Transmission of venous hypertension to the hypogastric vessels leads to venous congestion of the pelvic veins around the bladder causing haematuria as in this patient. The venous pressure increase may be regional and restricted to the venous system below the aneurysm as in this patient (Brewster et al, 1977).

The abdominal aortic aneurysm was successfully treated with an endovascular repair which sealed the fistula communication. BJHM

Brewster DC, Leslie WO, Darling RC (1977) Haematuria as a sign of Aorto-Caval Fistula. *Ann Surg* **186**(6): 766–71

Figure 1. Computed tomography angiogram showing communication between aorta and inferior vena cava. Red arrow: abdominal aortic aneurysm; solid white arrow: site of fistula between abdominal aortic aneurysm and inferior vena cava; dotted white arrow: arterial contrast opacifying the inferior vena cava.