Fever on an airline flight: a diagnostic challenge
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Case presentation
A 62-year-old man became acutely unwell with a fever on his flight home from a holiday in Bangladesh. Upon arrival in the UK he was admitted to a local hospital, febrile (40°C) but haemodynamically stable, with a cough, severe myalgia, lethargy and generalized weakness; he proceeded to rapidly lose weight. His only medical history was coronary artery disease. He had no known prior tuberculosis (TB) exposure.

Initial investigations revealed marked inflammation: CRP 250 mg/l, ESR 102 mm/h, anaemia (haemoglobin 79 g/l), neutrophilia (32 × 10⁹/l), eosinophilia (1.3 × 10⁹/l), thrombocytosis (536 × 10⁹/l), hypoalbuminaemia (9 g/l) and polyclonal IgG 32 g/l [normal range (NR) 6.00–16.00 g/l]. Liver and renal function were normal (creatinine 80 l mol/l). Low-level or trace blood and protein was present in his urine, consistent with his heightened inflammatory state. He was commenced on broad-spectrum antibiotics for a presumed bacterial infection, although subsequent chest radiograph and blood and urine cultures were all normal. Despite 4 weeks of antibiotics, his temperature and inflammatory markers failed to improve. During this period, screening for atypical respiratory viruses, parasites, malaria, TB, viral hepatitis and HIV were all negative. CT imaging of his chest, abdomen and pelvis showed only subtle peripheral lung reticulation suggestive of mild usual interstitial pneumonia (UIP). In the context of his elevated polyclonal IgG he had modest IgG₄ elevation [6.4 g/l (NR 0.00–1.3)] and weakly positive MPO-ANCA [11 IU/ml (NR 0.0–3.4)] and RF [45 IU/ml (NR 0–14)]. Cryoglobulins, ANA and complement levels were negative or normal.

In view of his failure to respond to antibiotics, a renal biopsy was performed to further consider his weak MPO-ANCA, which was initially thought to be spurious in the context of his marked polyclonal IgG. Consistent with his minimal urine sediment, normal glomeruli (no glomerulonephritis) were seen on light microscopy. A plasma cell tubulointerstitial infiltrate was present along with fibrinoid necrosis of a single interlobular artery (extraglomerular vasculitis) with surrounding granulomatous inflammation. Standard immunohistochemical stains were negative, however, subendothelial glomerular deposits were identified on electron microscopy, suggestive of an uncharacterized immune complex process. Taken together, the biopsy features were not typical of primary systemic vasculitis and were more suggestive of a medium or small vessel extraglomerular vasculitis secondary to a probable infective process. The interstitial infiltrate and granulomatous inflammation were concerning for IgG₄ disease or TB, however, biopsy stains for both IgG₄ and Ziehl-Neelson were negative. The uncharacterized subendothelial deposits also raised concern for an infectious immune complex-driven process.

He was referred to our centre for further management. In the absence of immediate organ-threatening vasculitis, glucocorticoids were withheld until a CT-PET was performed that found no deep infection, malignancy or large vessel inflammation. A CT aortogram showed normal large and medium arteries, which along with the MPO-ANCA suggested that the extraglomerular...
vasculitis was a small rather than medium vessel subtype. The atypical renal biopsy features and marked systemic inflammation were suspicious for an undiagnosed initial infectious trigger. However, having excluded ongoing infection, treatment with intravenous prednisolone and rituximab was commenced, alongside prophylactic isoniazid and pyridoxine to prevent potential reactivation of latent TB, given his frequent travel to higher-risk countries. His symptoms immediately responded to high-dose glucocorticoids (Fig. 1). He continued to receive rituximab every 6 months and 5 mg prednisolone daily as remission maintenance therapy and 1 year after presentation he remains well, in remission with normal renal function and inflammatory markers and stable mild UIP.

Discussion

We present a case of MPO-ANCA small vessel vasculitis with mild renal and lung involvement and atypical rapidity of onset and extreme inflammatory response. The atypical clinical features and lack of overt organ-threatening disease provided both diagnostic uncertainty and the opportunity for thorough investigation to rule out alternative diagnoses and secondary causes.

Diagnosing vasculitis can be challenging. Systemic vasculitis may be primary or secondary to other conditions such as infection, drugs and malignancy [1]. Vasculitis can be small, medium or large vessel disease, with small vessel further subdivided into ANCA-associated and immune complex vasculitis. Differentiating small vessel vasculitis (SVV) from other vasculitides or immune diseases as well as mimics/coexisting diagnoses, including malignancy and severe bacterial infection, particularly infective endocarditis and TB, is important, as treatments differ significantly [2].

The diagnosis of SVV is based on a combination of clinical symptoms and signs, serology (including ANCA), radiological findings and histology [3]. In our case, the acute onset and extreme level of systemic inflammation were dominant features, atypical for vasculitis and concerning for infection as the primary diagnosis. The significance of minimally active urinary sediment, subtle features of UIP (a more recently recognized feature of MPO–ANCA-associated vasculitis), low-titre MPO-ANCA and RF positivity (initially thought to be spurious in the context of polyclonal elevated IgG) were initially not recognized [4, 5]. Furthermore, the abrupt onset of symptoms on return from Bangladesh (one of the eight countries accounting for two-thirds of the global TB cases) [6] made TB a significant concern.

Tissue biopsy is considered the gold standard for the diagnosis of SVV [7]. In our patient, the kidney biopsy provided definitive evidence of extraglomerular vasculitis

![Renal histology](https://academic.oup.com/rheumatology/article/60/Supplement_3/iii21/6302219)
but also demonstrated atypical features, which interpreted in clinical context ultimately led to a diagnosis of ANCA-associated vasculitis, with a probable infective trigger. Additional histological stains allowed exclusion of TB, IgG4-related disease and cryoglobinaemia—key differential diagnoses.

In complex vasculitis cases with atypical features, a thorough diagnostic workup to exclude infection and malignancy is important. Histology remains the gold standard for diagnosis but must be interpreted in a clinical context. Treating any underlying cause as well as the vasculitis is important. The timing of therapy initiation requires careful consideration. At first presentation it is important to ensure correct diagnosis before treatments affect investigation results. Diagnostic information should be gathered quickly, facilitated by early involvement of multispeciality teams. In organ- or life-threatening vasculitis, treatment cannot be delayed and early treatment with glucocorticoids and immunosuppression is advised.

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Data availability statement

The data underlying this article will be shared on reasonable request to the corresponding author.

References

1 Jennette JC, Falk RJ, Bacon PA et al. 2012 revised International Chapel Hill Consensus Conference nomenclature of vasculitides. Arthritis Rheum 2013;65:1–11.

2 D’Cruz D. i107 Vasculitis mimics. Rheumatology 2018;57(Suppl 3):key075.107.

3 JCS Joint Working Group. Guideline for management of vasculitis syndrome (JCS 2008): digest version. Circ J 2011;75:474–503.

4 Watanabe T, Minezawa T, Hasegawa M et al. Prognosis of pulmonary fibrosis presenting with a usual interstitial pneumonia pattern on computed tomography in patients with myeloperoxidase anti-neutrophil cytoplasmic antibody-related nephritis: a retrospective single-center study. BMC Pulm Med 2019;19:194.

5 Baqir M, Yi EE, Colby TV et al. Radiologic and pathologic characteristics of myeloperoxidase-antineutrophil cytoplasmic antibody-associated interstitial lung disease: a retrospective analysis. Sarcoidosis Vasc Diffuse Lung Dis 2019;36:195–201.

6 World Health Organization. Global tuberculosis report 2020. Geneva: World Health Organization, 2020. Licence: CC BY-NC-SA 3.0 IGO.

7 Berden AE, Ferrario F, Hagen EC et al. Histopathologic classification of ANCA-associated glomerulonephritis. J Am Soc Nephrol 2010;21:1628–36.