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Exceptional Case

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Anti-neutrophil cytoplasmic antibody vasculitis presenting with bilateral renal vein thrombosis

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Abstract
We report a case of anti-neutrophil cytoplasmic antibody (ANCA)-associated necrotizing crescentic glomerulonephritis presenting with bilateral renal vein thrombosis and pulmonary emboli in a patient who also had a lupus anticoagulant and anti-cardiolipin antibodies. Although the link between venous thrombosis and ANCA vasculitis is well established, the coexistence of renal vein thrombosis is unusual. Furthermore, despite the positive ANCA, he was initially negative for antibodies to myeloperoxidase (MPO) and proteinase-3 (PR3), illustrating that a positive ANCA may be significant despite a negative test for antibodies to MPO and PR3.

Keywords: ANCA; anti-phospholipid; crescentic glomerulonephritis; renal vein thrombosis

Background

A link between venous thromboembolism (VTE) and anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is well established. The WeCLOT study was a prospective observational study of patients with Wegener's granulomatosis [1]. This showed an incidence of VTE of 7 per 100 patient years, which is significantly higher than that described for normal population cohorts or for patients with rheumatoid arthritis or systemic lupus erythematosus. In addition, Weidner *et al.* [2] reported that 13 of 105 patients with active AAV had thromboembolic events during the period of active disease. Seven of these had pulmonary emboli and 3 had iliac and/or caval vein thrombosis. None of the 13 patients had typical risk factors for VTE. More recently, a retrospective study confirmed an increased risk of developing VTEs at 1.8 per 100 patient years overall, increasing to 6.7 during active disease, which also appeared independent of classic risk factors [3]. None of these patients had renal vein thrombosis and we are not aware of any previous reports of this. A novel contributing mechanism to VTE has been demonstrated in AAV patients, which together with the increased endothelial activation could increase the risk of VTE. Antibodies against plasminogen antibodies and tissue plasminogen activator antibodies were found in the plasma of AAV patients and caused functional inhibition of fibrinolysis *in vitro* [4].

Case report

A 24-year-old Afro-Caribbean man presented with a 4-week history of fever, night sweats and abdominal pain associated with some weight loss and loose stools. On admission, his serum creatinine was 220 μmol/L with a urine protein–creatinine ratio (PCR) of 306 mg/mmol. The serum albumin was 34 g/L and C-reactive protein (CRP) was raised at 121 mg/L. His urinalysis revealed haematuria (4+) and he had an atypical ANCA but was negative for antibodies to both myeloperoxidase (MPO) and proteinase-3 (PR3). Serum protein electrophoresis showed a reduced albumin but no increase in α2-macroglobulin or other abnormality. A renal ultrasound showed normal-sized kidneys, and in view of his fever and abdominal pain, he underwent a computed tomography scan. Unexpectedly, this revealed bilateral pulmonary emboli and bilateral renal vein thrombosis as shown in Figure 1.

His initial thrombophilia screen showed a lupus anticoagulant (LA) by dilute-activated partial thromboplastin time analysis with negative anti-cardiolipin antibodies (aCL). His activated partial thromboplastin time was normal at 1.1. The acute kidney injury was felt to be due to the renal vein thrombosis for which he was anticoagulated, initially with heparin and then with warfarin, and discharged. A month after his initial presentation, he was re-admitted with vomiting, possibly secondary to warfarin intolerance, and a subtherapeutic international normalised ratio requiring intravenous unfractionated heparin. His renal function was unchanged with a serum creatinine of 180 μmol/L, CRP was now <5 mg/L, urine PCR was 363 mg/mmol and serum albumin 32 g/L. A decision was made to perform a renal biopsy. There were 20 glomeruli of which 3 were obsolete. The remainder showed 1 active and 15 fibrocellular crescents. Tubular atrophy was in 10% of the sample and immunoperoxidase staining was negative for all immunoglobulin and complement components. There were no features suggestive of anti-phospholipid syndrome (APLS). Representative histology is shown in Figure 2.

The possibility of immunosuppression was considered. However, at this point, his serum creatinine fell progressively

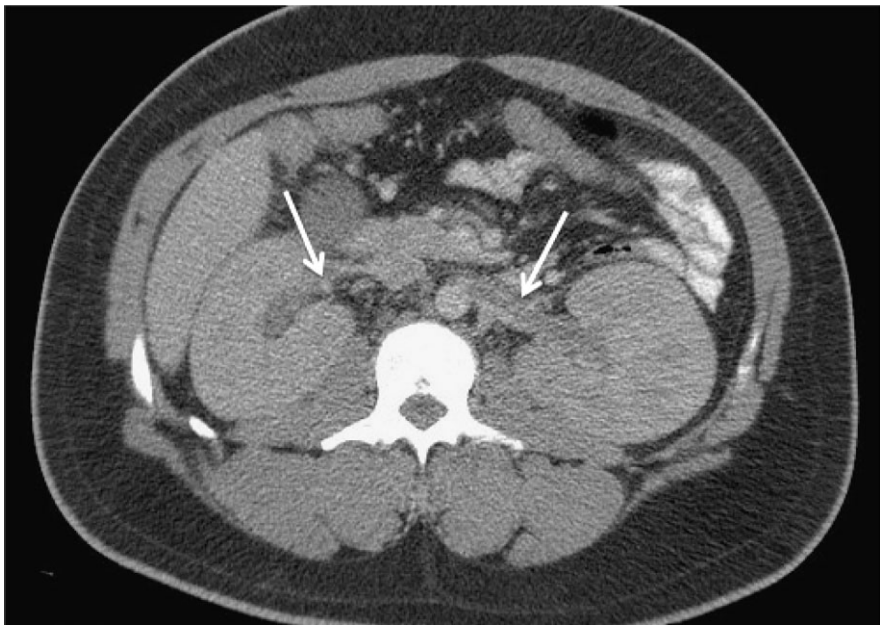

Fig. 1. Computed tomography with contrast showing thrombus within both renal veins (white arrows).

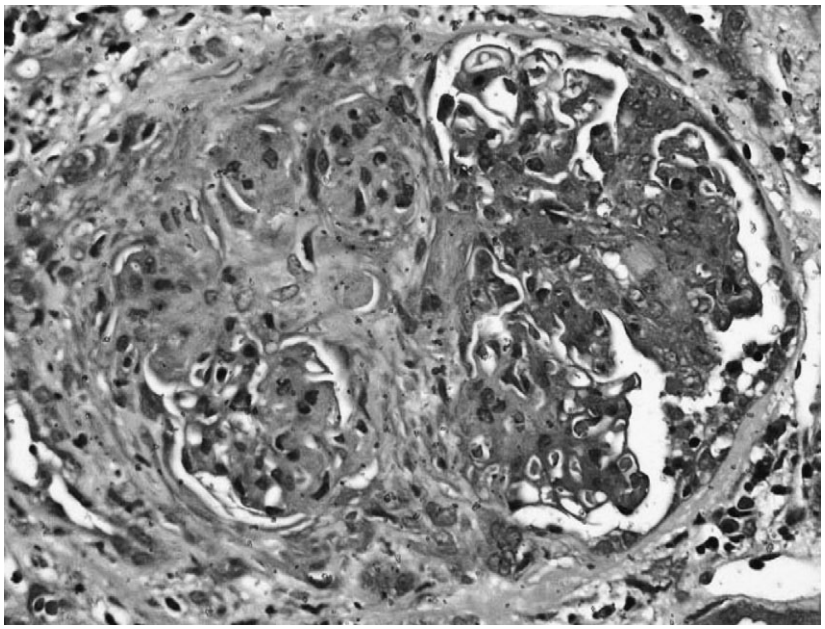

Fig. 2. Renal histology showing a representative glomerulus with a fibrocellular crescent.

and, 2 months after the renal biopsy, was in the normal range at 102 μmol/L, where it stayed for the next 5 months. In view of this, and the fact that the renal biopsy had shown largely inactive lesions, he was not given immunosuppression. The possibility of another renal biopsy was being considered to assess if there were any active lesions but he then failed to attend clinic and, despite considerable efforts to contact him, was lost to follow-up. He re-presented 28 months after initial presentation with irreversible kidney damage, which was confirmed on another renal biopsy. The renal veins were not visible on ultrasound and further imaging was not performed. He has been on haemodialysis since. He has remained ANCA positive, and his anti-MPO and PR3 levels were repeated with an alternative assay. Although these had previously been negative using the Phadia ELiA® assay, he was MPO positive with the FIDIS Luminex® assay. His LA has been confirmed and, although aCL were negative at initial presentation, they were later found to be positive on more than one occasion. He has had no further thrombotic events during follow-up though has remained on anticoagulants.

Discussion

This is the unusual case of AAV presenting with pulmonary emboli and bilateral renal vein thrombosis. Although not appreciated on the initial tests, he was in fact positive for

antibodies to MPO on further testing. He also had a positive LA and aCL.

An increased incidence of LA and aCL has been described in systemic vasculitis with 25 of 144 patients positive for one of these tests at one time and 9 of these having clinical APLS [5]. It is not clear if AAV itself predisposes to the development of the APLS or if AAV develops as a result of APLS. However, a very small proportion of APLS patients have AAV, so, the former seems more likely. In this patient, the procoagulant state due to the presence of anti-phospholipid antibodies and AAV combined to cause renal vein thrombosis and pulmonary emboli. It should be noted that renal vein thrombosis is most commonly seen with either malignancy or the nephrotic syndrome. In one single-centre series of 218 patients with renal vein thrombosis, 143 had malignancy and 43 had nephrotic syndrome [6]. Only 36 patients in this study underwent thrombophilia screening, making conclusions on a link between renal vein thrombosis and LA or aCL difficult. We do not know the degree of his proteinuria prior to his renal vein thrombosis but nephrotic range proteinuria is unusual with renal AAV and would be unlikely given the later findings on renal biopsy. His initial serum albumin was 34 g/L but this was in the context of an inflammatory response, which would have lowered his albumin further. Nonetheless, it is possible that his proteinuria represented an additional risk factor for thrombosis.

This case illustrates the known link between AAV and VTE and emphasizes that other risk factors for venous thrombosis such as anti-phospholipid antibodies may add to the procoagulant state in AAV. The coexistence of an LA and aCL led to renal vein thrombosis, which is otherwise predominantly seen in patients with malignancy or the nephrotic syndrome. In addition, a positive ANCA with negative anti-MPO or PR3 assays may still be significant, as our patient was positive for anti-MPO antibodies when tested with a second assay. Finally, the progression to end-stage kidney disease emphasizes the importance of close monitoring for all patients with AAV.

Conflict of interest statement. None declared.

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