CASE REPORT

Tuberculosis and pauci-immune crescentic glomerulonephritis

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SUMMARY

We report here a case that highlights tuberculosis (TB) as a possible cause for pauci-immune crescentic glomerulonephritis (c-GN), an important and often treatable cause of kidney injury. A 47-year-old HIV-negative man of mixed ethnicity presented with a 2-week history of cough, haemoptysis and unintentional weight loss. Chest examination revealed crepitations over the right upper zone and urinalysis demonstrated an active urinary sediment with red cell casts. Chest radiograph confirmed right upper lobe cavitation. Serum laboratory investigations revealed a serum creatinine of 632 µmol/L and were negative for antineutrophil cytoplasmic antibodies. A diagnosis of pauci-immune c-GN was made on renal biopsy. In addition, sputum PCR confirmed infection with drug-sensitive *Mycobacterium tuberculosis*. Standard TB treatment and immunosuppression with prednisone and cyclophosphamide was commenced, and over the course of 6 months, renal function improved to an estimated glomerular filtration rate >60 mL/min.

immune complex-mediated glomerulonephritis^{5–7} and antiglomerular basement membrane disease.⁸ Furthermore, TB has been associated with extra-renal manifestations of AAV⁹ and ANCA-negative leucocytoclastic vasculitis.¹⁰ We report here a case that highlights TB as a cause for pauci-immune c-GN.

CASE PRESENTATION

A 47-year-old man of mixed ethnicity presented with frank haemoptysis and a 2-week history of cough associated with unintentional weight loss. He had a history of heavy cigarette smoking and ethanol use but no recreational or intravenous drug use. There was no history of occupational exposure to nephrotoxins.

Examination revealed a pale, normotensive, thin man with multiple tattoos. There was no rash or arthritis nor was there lymphadenopathy, clubbing or signs of chronic liver disease. Crepitations and wheezes were heard over the right upper zone of his chest. Cardiovascular, abdominal and neurological examinations were normal.

BACKGROUND

Tuberculosis (TB) is a major global threat and a leading cause of death due to infectious disease.¹ In adults, rapidly progressive glomerulonephritis (RPGN), due to crescentic glomerulonephritis (c-GN), usually occurs in the context of an antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV).² The unfortunate coincidence of TB and c-GN in the same patient has been described in association with rifampicin.^{3,4}

INVESTIGATIONS

Chest radiography revealed a confluent opacification of the right upper lobe with areas of cavitation (see figure 1), suggestive of pulmonary TB. Sputum PCR collected on admission (GeneXpert MTB/RIF; Cepheid, Sunnyvale, California, USA) was positive for *Mycobacterium tuberculosis* sensitive to rifampicin. The urine dipstick revealed 2+ blood and 3+ proteinuria and red cell casts were noted on urine microscopy. The initial serum creatinine was 632 µmol/L (7.15 mg/dL) and an HIV rapid test (Alere Determine HIV-1/2 Ag/Ab Combo) was negative. The working diagnosis was active pulmonary TB with acute kidney injury. However, in view of the active urine sediment and the lack of a convincing explanation for the acute kidney injury, renal biopsy was performed. The renal biopsy revealed multiple cellular crescents involving 50% of the 22 glomeruli visualised, with areas of segmental necrosis (see figure 2). No granulomas were observed. Immunohistochemistry (IgG, C3, IgA and IgM) was negative in keeping with a pauci-immune crescentic glomerulonephritis.

Further laboratory testing followed: proteinase-3 and myeloperoxidase ANCA ELISA's (Quanta Lite™ MPO/PR3, Inova Diagnostics, San Diego, California, USA) were negative. Antinuclear factor and syphilis testing was negative and serum

Figure 1 Posterior anterior chest radiograph.

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Figure 2 Renal biopsy; cellular crescent in Bowman's space.

complement levels were normal. The hepatitis B surface antigen test was positive with negative e-antigen and the quantitative hepatitis B viral load was lower than detectable limit (COBAS AmpliPrep/COBAS TaqMan HBV Test, V.2.0, Roche Molecular Systems, Branchburg, New Jersey, USA). Hepatitis C antibodies were negative. Six days later, the sputum TB culture became positive, and the organism was sensitive to both rifampicin and isoniazid.

TREATMENT

A diagnosis of ANCA-negative pauci-immune c-GN was made and the patient was commenced on combination TB treatment including rifampicin, isoniazid, pyrazinamide and ethambutol followed by three consecutive daily methylprednisolone pulses of 500mg each, a tapering course of oral prednisone and 6 monthly intravenous cyclophosphamide doses of 750mg/m². Prophylactic oral lamivudine was also started prior to immunosuppression to prevent hepatitis B flare.

OUTCOME AND FOLLOW-UP

After 6 months of treatment, the patient's clinical and biochemical parameters had improved (see [table 1](#)) and immunosuppression was discontinued. The creatinine settled to a baseline of 99 µmol/L (1.12mg/dL) with estimated glomerular filtration rate >60 mL/min (Modification of Diet in Renal Disease formula) after a further 8 months off immunosuppression. Antituberculous chemotherapy was continued for a total of 12 months. He has remained in complete remission until the present day with subsequent ANCA testing remaining negative.

DISCUSSION

There are three major mechanisms for RPGN,¹¹ classified on the basis of direct immunofluorescence/immunohistochemistry. Between 10% and 20% of patients with RPGN have anti-glomerular basement membrane (anti-GBM) disease. This is characterised by the presence of linear deposition of IgG anti-GBM antibodies along the GBM. The second mechanism, responsible for approximately

Table 1 Biochemical results, tests and interventions												
	21/06/2013	22/06/2013	28/06/2013	03/07/2013	10/07/2013	20/08/2013	12/11/2013	10/12/2013	07/01/2014	04/02/2014	11/09/2014	9/10/2014
Comment	Results on presentation	GeneXpert positive: commenced TB treatment	Methyl prednisone 500 mg×3/7 for 6 months		commenced cyclophosphamide	commenced monthly						
White cell count (×10 ⁹ /L/x 10 ³ /µL)	13.31			12.64	13.16			8.62	7.93	8.54	12.73	11.78
Haemoglobin g/L (g/dL)	12.5			78 (7.8)	104 (10.4)			137 (13.7)	148 (14.8)	149 (14.9)	138 (13.8)	150 (15.0)
Urea mmol/L (mg/dL)	20.3 (56.87)						4.5 (12.61)	7.4 (20.73)	4.5 (12.61)			
Creatinine µmol/L (mg/dL)	632 (7.15)			358 (7.22)	138 (1.56)		112 (1.27)	115 (1.3)	121 (1.37)	126 (1.43)	101 (1.14)	99 (1.12)
Urine protein creatinine ratio g/mmol	0.131			0.08	0.07		0.03	0.02	0.018	0.03	0.015	0.02
TB, tuberculosis.												

40% of RPGN, is immune complex-mediated disease and is characterised by granular deposition of immune complexes in the glomeruli.¹² We present here a case of pauci-immune ANCA negative c-GN occurring in a patient with pulmonary TB.

Most patients with pauci-immune c-GN test positive for ANCAs directed at either myeloperoxidase or proteinase 3 antigens present on the surface of neutrophils.¹³ While the majority also have systemic small vessel vasculitis, the disease is confined to the kidney in approximately one quarter of cases.² Approximately 10% of those with pauci-immune c-GN are found to be ANCA negative,¹³ provided both ELISAs and indirect immunofluorescence testing is used.¹⁴ ANCA-negative pauci-immune glomerulonephritis appears similar in histology, treatment response and outcome to myeloperoxidase (MPO)-ANCA vasculitis.¹⁵ It has also been documented that serum factors such as ceruloplasmin may mask MPO epitopes.¹⁶

The renal biopsy findings in our patient revealed cellular crescents, areas of focal necrosis, absence of granulomas and a paucity of immune complex deposition. These findings, in conjunction with sparing of the upper respiratory tract, point away from a diagnosis of granulomatosis with polyangiitis. Our patient was also diagnosed with *M. tuberculosis* infection, raising the question of an association between these two disease entities. Multiple associations between non-crescentic immune complex-mediated glomerulonephritis and *M. tuberculosis* have been reported.^{6 17 18 18–20} Non-tuberculous mycobacteria have also been associated with immune complex mediated glomerulonephritis.²¹ In addition, rifampicin has been implicated in the development of a crescentic immune complex-mediated glomerulonephritis.³ Only rarely has an association between c-GN and *M. tuberculosis* been described. Three of these cases revealed an immune complex-mediated pattern of injury (granular immunofluorescence staining),^{5–7} and the forth revealed an anti-GBM pattern of injury (diffuse linear immunofluorescence staining).⁸

While the aetiology of AAV remains unclear, various genetic, chemical, haematological and infective factors have been implicated in its pathogenesis. With regard to infective factors, certain subtypes of *Staphylococcus aureus* may contribute to the induction and persistence of AAV. Proposed mechanisms include molecular mimicry, the recognition of specific pathogen-associated molecular patterns, increased expression of neutrophil extracellular traps and superantigen-induced T and B cell activation.^{22 23} In the case of

active tuberculous infection, cytokine activation of neutrophils may result in expression of ANCA antigens on their cell membranes.²⁴ ANCAs directed against those antigens could bind to the neutrophil membrane antigens and result in degranulation and injury to the vascular endothelium.

To our knowledge, hepatitis B has only been associated with an immune complex mediated pattern of glomerular injury. Since our patient presented with a pauci-immune pattern of injury and had an undetectable hepatitis B viral load, we do not consider the hepatitis B infection to be causative.

The patient responded well to the 6-month course of cyclophosphamide infusions and tapered prednisone. Although maintenance immunosuppression with azathioprine would often be indicated in pauci-immune c-GN, we did not consider this necessary in this case because the patient was ANCA negative and the inciting agent (TB) had been fully treated. Fortunately, the patient has remained in remission to date and repeat ANCA serology testing by immunofluorescence and ELISA has also remained negative.

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Contributors All three authors were involved in management of this case as well as analysis and interpretation of data. JOO wrote the first draft and critical appraisal was performed by JE and RF.

Competing interests None declared.

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Learning points

- The main learning point in this case was the apparent association between pulmonary tuberculosis (TB) and the development of pauci-immune crescentic glomerulonephritis (c-GN).
- TB has been associated with several forms of kidney injury. Clinicians should be mindful of these associations and have a low threshold to consider renal biopsy in the context of TB and renal dysfunction.
- The final point of interest was the therapeutic dilemma faced in this case. Intensive immunosuppression is relatively contraindicated in the context of active TB. On the other hand, untreated c-GN is likely to result in a very poor renal outcome. Case reports have shown good outcomes in patients with rapidly progressive glomerulonephritis treated with both immunosuppression and antituberculous treatment.^{6 8} Fortunately, our patient responded well to both therapies.

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