Rare immune-mediated pneumonitis in association with post-streptococcal glomerulonephritis

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Abstract
We describe the case of a 48-year-old man with an acute nephritis and respiratory failure. Clinical history, streptococcal antibody titres and renal biopsy led to a diagnosis of post-streptococcal glomerulonephritis. Respiratory investigations excluded pulmonary oedema and infection. We hypothesize that this man had a co-existing post-streptococcal glomerulonephritis and an immune-mediated pneumonitis. This is a very rare association, which was last described in 1982.

Keywords: glomerulonephritis; pneumonitis; post-streptococcal

Background
Infection with Group A Streptococcus is known to produce immunologically mediated phenomena, including rheumatic fever and post-streptococcal glomerulonephritis. A streptococcal infection can precede the development of a glomerulonephritis by 1–12 weeks [1]. The pathology is one of a planted antigen in the glomerulus with subsequent production of in situ immune complexes altering the permeability of the glomerular basement membrane [2]. In addition, the streptococcal antigen is hypothesized to be pathogenic by cross-reacting with glomerular structures and directly activating complement [3]. However, the precise mechanisms by which antigen, molecular mimicry, autoimmunity, immune complex deposition and predisposing host factors lead to a clinical glomerulonephritis have yet to be defined [4]. In the UK, the incidence of infection with Group A Streptococcus is above expected levels [5]. The immunological sequelae of Group A streptococcal infection may consequently become more common in clinical practice.

We present the case of a 48-year-old male who presented with co-existing post-streptococcal glomerulonephritis and respiratory failure. We hypothesize that he had a post-streptococcal immune-mediated pneumonitis.

Case report
A 48-year-old Caucasian male presented with breathlessness and ankle swelling. He was a naval serviceman with no significant medical history and a navy medical 3 years previously had been unremarkable. He was a life-long non-smoker who undertook regular exercise. He had attended his general practitioner 10 days prior to presentation with a sore throat and cough. He had received a course of oral amoxicillin but had continued to deteriorate with increasing breathlessness upon minimal exertion.

On admission to hospital, he was dyspnoeic with a sinus tachycardia. His blood pressure measured 205/113 mmHg and his jugular venous pressure (JVP) was visible at the angle of the jaw. Heart sounds were normal. Auscultation of his chest was unremarkable with vesicular breath sounds only. He had marked peripheral oedema of the legs and trunk. Fundoscopy was normal. Pulse oximetry demonstrated saturations of 95% on air falling to 85% with exertion. Arterial blood analysis showed a pO2 of 9.2 kPa. Bedside echocardiography was normal. Blood tests revealed a neutrophilia of 10.9 $10^9$/L, a raised C-reactive protein of 150 mg/L and a low albumin of 26 g/L. Creatinine was 91 $\mu$mol/L. The patient was empirically treated for an atypical pneumonia with co-amoxiclav and clarithromycin. When he failed to improve, cotrimoxazole 120 mg/kg/day and furosemide 80 mg daily were added.

A chest radiograph and high-resolution computerized tomography (CT) imaging (Figure 1) demonstrated perihilar infiltrates with peripheral sparing. Bronchoscopy excluded pulmonary haemorrhage with no evidence of vasculitis or granulomata on transbronchial biopsies. Bronchoalveolar lavage revealed no significant bacterial infection.
Immunofluorescence for common respiratory viruses and testing for *Pneumocystis jirovecii* were both negative. Blood cultures were sterile and antibiotics were discontinued after 7 days. Corticosteroids were not administered.

Urine testing revealed microscopic haematuria and proteinuria. Proteinuria was in the nephrotic range with a protein-creatinine ratio (PCR) of 414 mg/mmol and a measured urinary protein concentration of 4.5 g/L. Complement measurements demonstrated a borderline C3 of 0.16 g/L (0.16–0.38 g/L) and a low C4 of 0.43 g/L (0.79–1.52 g/L). Anti-neutrophil cytoplasmic antibody and anti-glomerular basement membrane antibody were negative. Serum creatinine peaked at 136 μmol/L [estimated glomerular filtration rate (eGFR) 45 mL/min/1.73m²]. Hypertension was treated with ramipril and bisoprolol in addition to the furosemide and the patient underwent renal biopsy.

Renal histology showed an acute, exudative, endocapillary glomerulonephritis without crescents with diffuse mesangial proliferation and polymorphs in the glomerular tufts. Immunoperoxidase staining on formalin-fixed paraffin-embedded tissue sections revealed C3 and C1q deposition in a subendothelial and mesangial distribution. Electron microscopy demonstrated epithelial foot process effacement, subepithelial electron-dense hump-like deposits and smaller subendothelial and mesangial electron-dense deposits (Figure 2). A diagnosis of post-infectious glomerulonephritis was made. An anti-streptolysin O titre of 800 U/mL (<200 U/mL) and an anti-DNase B titre of 1600 U/mL (<200 U/mL) confirmed recent exposure to Group A Streptococcus.

Nine days after admission, the patient had improved with effective management of his hypertension, spontaneous regression of his nephrosis and improved oxygenation. One month later, he was no longer nephrotic with a PCR of 30 mg/mmol. Serum albumin had improved to 32 g/L from a nadir of 20 g/L and the patient had resumed a military fitness regimen. The serum creatinine remained stable at 88 μmol/L although urine showed ongoing microscopic haematuria. Anti-hypertensive treatment was still required with a combination of three agents but diuretics were no longer needed. The perihilar infiltrates on chest radiograph showed improvement but residual radiographic changes persisted despite his now euvolaemic state following fluid weight loss of 17 kg. Complement levels had normalized.

**Discussion**

The presenting feature of this case was severe dyspnoea with unusual and striking radiological changes. The patient had many features of an acute nephritic syndrome with marked hypertension, elevated JVP, peripheral oedema and microscopic haematuria. Co-existing nephrotic-range proteinuria was also present. There was only a modest reduction in eGFR associated with diuresis and anti-hypertensive treatment.

We hypothesize that the patient had developed a post-streptococcal pneumonitis as well as his biopsy-proven glomerulonephritis. This produced a striking perihilar pattern of infiltration on chest imaging. Given the clinical picture of fluid overload, pulmonary oedema was a possible differential diagnosis. However, the CT scan demonstrated an infiltrate denser than that seen with oedema and the patient’s radiological signs were slow to resolve despite a comparably rapid correction in the patient’s fluid state. An infective aetiology was excluded as the clinical signs were not consistent with a bilateral pneumonia, empirical antibiotics did not alter the disease course and cultures of blood and bronchoalveolar lavage fluid were sterile. Pulmonary haemorrhage was excluded on bronchoscopy.

An ‘uncommon pneumonia’ has been previously described in conjunction with post-streptococcal glomerulonephritis. In a series of 184 Romanian patients with post-streptococcal glomerulonephritis, three patients had nephritis, dyspnoea, variable pulmonary signs and a defining radiological picture including that of bilateral opacities. Infection, fluid overload and pulmonary haemorrhage failed to explain the complete clinical picture. Pneumonitis secondary to an immune response to the streptococcal antigen was therefore postulated [6].

Published literature suggests that, even without a co-existing nephritis, post-streptococcal pneumonitis itself is very rare. In
a review of 188 published cases of post-streptococcal arthritis from 1982 to 2002, only two cases of pulmonary infiltrate were described [7, 8]. References to post-streptococcal pleuritis in the literature remain supported by work from 1928 [9]. This highlights the exceptional rarity of the clinical case described here.

Conflict of interest statement. None declared.

References


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