

Pneumococcal glomerulonephritis in a healthy child: a case report and literature review

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ABSTRACT Pneumococcal glomerulonephritis is rarely described in the literature. We report a four-year-old boy who developed acute glomerulonephritis following pneumococcal bacteraemia and submandibular lymphadenitis, and review the published literature. Two weeks after developing acute glomerulonephritis, the patient developed bronchopneumonia with left pleural effusion. However, by the fourth week of admission, his renal function had normalised and lung involvement resolved.

Keywords: glomerulonephritis, pleural effusion, pneumonia, *Streptococcus pneumoniae*

INTRODUCTION

Nephritogenic strains of group A β -haemolytic streptococci (GABHS), such as *Streptococcus (S.) pyogenes*, are the most common cause of post-infectious acute glomerulonephritis (AGN) following throat or skin infections. Isolated reports of acute nephritis caused by *S. pneumoniae* infection, usually following respiratory symptoms, have rarely been described.^(1,2) Herein, we present a previously healthy child who developed pneumococcal AGN following submandibular and cervical lymphadenitis complicated with respiratory problems, and in whom AGN was confirmed on blood culture. We also review the relevant literature.

CASE REPORT

A previously healthy four-year-old boy presented to Hospital Kuala Lumpur, Malaysia, with a one-week history of fever and neck swelling. Two days prior to admission, he developed high fever, vomiting and diarrhoea, with poor oral intake and reduced urine output. On examination, the boy was lethargic, febrile (temperature at 39.9°C) and appeared ill. His pulse rate was 120 bpm, respiratory rate was 30 bpm and blood pressure was 98/46 mmHg (50th percentile for age, gender and height at 93/50 mmHg). The patient was noted to have bad dental caries, cracked lips and dry mucous membrane with otherwise warm peripheries and normal capillary refilling time. There were enlarged, tender and non-fluctuant left submandibular (3 cm \times 3 cm) and submental (2 cm \times 1 cm) lymph nodes. He also had multiple bilateral cervical lymphadenopathies and a 3-cm hepatomegaly. Physical examination was otherwise unremarkable. Past medical and family histories were insignificant, and immunisation was complete (Malaysia's routine immunisation programme does not include heptavalent pneumococcal conjugate vaccine).

Laboratory investigations showed elevated white blood cells (WBCs; 28.8 \times 10⁹/L) with neutrophilia (93.7%). Blood urea nitrogen (21.4 mmol/L) and serum creatinine (138 μ mol/L)

were also elevated. The other blood parameters investigated were haemoglobin (8.4 g/dL), platelets (399 \times 10⁹/L), C-reactive protein (5.20 mg/dL) and serum albumin (24 g/L; normal range 35–50 g/L). Serum complement C3 was at 0.21 g/L (normal range 0.55–1.20 g/L), while C4 was at 0.23 g/L (normal range, 0.20–0.50 g/L). Urinalysis and microscopic examination revealed 3+ proteins, numerous red blood cells (RBCs) and WBCs, with 2+ RBCs, 2+ WBCs and 2+ granular casts per high-powered field. Spot urine protein/creatinine index was 0.21 and 24-hour urine protein was at 25 mg/m²/hour. Results of the patient's liver function test were normal. Antistreptolysin O titre (ASOT) was elevated at 800 IU/mL (normal range, < 200 IU/mL). Quantitative immunoglobulins were normal and connective tissue studies were negative.

Initial chest radiography on admission was normal. The first blood culture grew *S. pneumoniae* sensitive to penicillin and cephalosporin. However, further tests for pneumococcal serotyping and minimal inhibitory concentration (MIC) were unavailable. Cultures from the patient's throat swab and urine were sterile. Renal ultrasonography demonstrated bilateral enlarged kidneys with increased echogenicity.

The patient's initial management was focused on the possible causes of cervical lymphadenitis. Intravenous (IV) penicillin (50,000 unit/kg/dose) and cefotaxime (50 mg/kg/dose) were commenced. Over the following 48 hours, the patient developed periorbital and leg oedema, with tea-coloured urine. The patient was subsequently treated for acute nephritis with fluid restriction, and put on a low-salt diet and close monitoring of daily fluid intake/urine output. His blood pressure remained stable throughout the course of hospitalisation.

Despite being administered antibiotics, the patient's fever remained unresolved. After two weeks of hospitalisation, he developed bronchopneumonia with left pleural effusion that was confirmed on repeat chest radiography. A left pleural tap did not grow any organisms, but the effusion did not deteriorate.

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Table I. Clinical and epidemiological data of patients reported to have pneumococcal glomerulonephritis in the literature.

Study, year	Age of patient (yrs)/gender/country	Nature of primary infection	Interval between primary infection and renal symptoms	Renal abnormalities on admission	Blood parameters	Chest radiography findings	Culture results	Treatment	Outcome
Hyman et al, 1975 ⁽⁴⁾	4/ F/ USA	Lower respiratory tract infection	2 days	Haematuria, proteinuria (300 mg/dL), pyuria, BP (90/60 mmHg)	BUN: 15 mmol/L SCr: 0.7 mg/dL C3/C4: reduced/normal ASOT: elevated	Right middle lobe pneumonia	Blood: <i>S. pneumoniae</i> serotype 14 Throat and urine: negative	Ampicillin (duration: NA)	Discharged on Day 5; normal renal function and complement levels at 8 wks; normal urinalysis at 7–8 mths
Kaehny et al, 1978 ⁽⁶⁾	40/ M/ USA	Bacteraemic left lower lobe pneumonia	9 days	Haematuria, azotaemia, oliguria	BUN: NA SCr: 2.4 mg/100 mL C3/C4: reduced/reduced ASOT: NA	Left lower lobe pneumonia; alveolitis and interstitial infiltrates at 2 wks	Blood: <i>S. pneumoniae</i> serotype 9	Penicillin G, prednisone × 7 wks, azathioprine × 3 wks	Discharged at 13 wks with microscopic haematuria and proteinuria; asymptomatic after 8 mths
Schacter et al, 1987 ⁽²⁾	5/ M/ Israel	High fever, macroscopic haematuria	24 hrs	Haematuria, proteinuria (0.9 g/m ² /hour), pyuria, oliguria, BP (150/100 mmHg)	BUN: 104 mmol/L SCr: 1.2 mg/dL C3/C4: reduced/normal ASOT: normal	Right lower lobe pneumonia	Blood: <i>S. pneumoniae</i> serotype 5	Ampicillin (duration: NA)	Normal renal function at discharge on Day 11; microscopic haematuria and proteinuria persisted for 1 yr
Wolach et al, 1990 ⁽³⁾	3.5/ M/ Israel	Left submandibular suppurative adenitis	12 days	Haematuria, proteinuria (60 mg/dL), BP (140/95 mmHg)	BUN: NA SCr: 1.2 mg/dL C3/C4: reduced/reduced ASOT: normal	Not assessed	Submandibular discharge: <i>S. pneumoniae</i> serotype 15 Throat: negative	Ampicillin; surgically drained submandibular abscess	Normal renal function at 6 wks
Lawlor et al, 1992 ⁽⁸⁾	56/ M/ USA	Right lower leg cellulitis	5 days	Haematuria, proteinuria (585 mg/24 hours), pyuria, BP (128/70 mmHg)	BUN: 61 mmol/L SCr: 1.9 mg/dL C3/C4: normal/normal ASOT: elevated	Normal	Bulla aspirate and blood: <i>S. pneumoniae</i> serotype 6B	Penicillin × 3 wks, daily wound debridement	Skin grafting; discharged at 7 wks
Phillips et al, 2005 ⁽¹⁾	6/ F/ USA	Lower respiratory tract infection	7 days	Haematuria, proteinuria, pyuria, spot urine protein/creatinine ratio 3.87, BP (125/68 mmHg)	BUN: 31 mmol/L SCr: 2.3 mg/dL C3/C4: reduced/reduced ASOT: NA	Left lingular pneumonia	Blood and urine: <i>S. pneumoniae</i> group 7	Ceftriaxone, diltiazem, lasix, renal diuresis	Normal renal function at 8 wks
Usmani et al, 2007 ⁽⁷⁾	Adult/ M/ USA	NA	NA	NA	NA	Pneumonia	Blood: <i>S. pneumoniae</i> serotype 7	Ceftriaxone, diltiazem, lasix, renal diuresis Pulse steroid × 5 days and renal dialysis	Normal renal function
Lechón et al, 2010 ⁽⁵⁾	4.25/ M/ Spain	Lower respiratory tract infection	3 days	Haematuria, pyuria, proteinuria (19.06 mg/m ² /hour), oliguria (0.73 mL/kg/hour), BP (107/72 mmHg)	BUN: 74 mmol/L SCr: 1.11 mg/dL C3/C4: reduced/normal ASOT: elevated	Left lower lobe pneumonia	Blood: <i>S. pneumoniae</i> serotype 17F Throat swab and urine: negative	Cefotaxime, lasix for oliguria	Normal renal function on discharge; normal C3 and no proteinuria at 7 wks; microscopic haematuria persisted for 5 mths
Present study, 2014	4/ M/ Malaysia	Left submandibular and cervical adenitis	7 days	Haematuria, pyuria, proteinuria (25 mg/m ² /hour), spot urine protein/creatinine ratio 0.21, oliguria, BP (98/46 mmHg)	BUN: 21.4 mmol/L SCr: 138 µmol/L C3/C4: reduced/normal ASOT: elevated	Normal on admission; pneumonia and left pleural effusion at 2/52	Blood: <i>S. pneumoniae</i> ; serotype: NA	Penicillin × 4 wks, cefotaxime × 1 wk	Discharged at 4 wks; normal renal function at 6 wks; pneumonia and left pleural effusion resolved by 4 wks

ASOT: anti-streptolysin O; BUN: serum blood urea nitrogen; C3: complement 3; C4: complement 4; Cr: serum creatinine; F: female; M: male; NA: not available; S.: *Streptococcus*

Repeat blood culturing to rule out possible nosocomial pneumonia was negative. After three weeks in the ward, the patient's fever settled and urine output was maintained at > 1 mL/kg/hour. IV penicillin was continued for a total of four weeks while cefotaxime was given for seven days.

Four weeks into hospitalisation, the patient's renal function normalised, with complete resolution of pneumonia and pleural effusion on chest radiography. He was discharged well one month after admission and remained in good health with normal renal function at the six-week follow-up. Repeat urinalysis revealed no microscopic haematuria or proteinuria. The moderate recovery of his renal status made renal biopsy unnecessary. Although he was advised further evaluation in view of the possibility of progressive renal disease, the patient subsequently defaulted follow-up, and we were unable to assess his long-term renal outcome and repeat C3 assessments.

DISCUSSION

The aetiological role of *S. pyogenes*, a GABHS, in childhood post-infectious AGN is well established.⁽¹⁾ Glomerulonephritis following infection by other microbial agents such as *S. pneumoniae* has rarely been described. Following a review of the English language literature, the authors found that only eight patients with pneumococcal glomerulonephritis (5 children, 3 adults) had been reported over the past 3–4 decades.^(1–8) The clinical and epidemiological characteristics of these eight patients are presented in Table 1.

For the patients reported in the literature to have pneumococcal glomerulonephritis, pneumococcal serotypes 5, 6B, 7, 9, 14, 15 and 17F^(1–8) have been described as nephritogenic strains. Similar to our patient, pneumococcal bacteraemia was reported for almost all of these other patients, suggesting that the rarity of pneumococcal glomerulonephritis could be attributed to the invasiveness of the pneumococcal infection itself. There was a preponderance of male gender (6 males, 2 females) and paediatric patients (n = 5) in all the eight aforementioned patients (mean age 11.8 [range 3.5–56] years). All patients, including ours, had microscopic haematuria, proteinuria and/or oliguria on admission. Most patients developed high blood pressure^(1–3,5) on presentation, but only two required diuretics,^(1,5) and only one of these patients needed antihypertensive agents.⁽¹⁾ Pneumococcal infections were treated with either ampicillin, penicillin or cephalosporin. The outcome of renal involvement in these patients ranged from self-limiting course to acute renal failure requiring dialysis^(1,7) and steroid treatment.⁽⁷⁾ Our patient had uneventful acute nephritis and a stable blood pressure throughout hospitalisation.

The average incubation period between GABHS infection and the development of AGN ranged between 1 and 2 weeks for patients with pharyngitis and 3–6 weeks for those with skin infections. Patients were usually no longer febrile at the onset of AGN. In patients with pneumococcal AGN, the onset of nephritis was seen within 2–10 days^(3,4,6,8) of the primary infection,

manifesting as pneumonia,^(1,2,4–7) submandibular suppurative adenitis⁽³⁾ or leg cellulitis.⁽⁸⁾

In our patient, who developed AGN one week after experiencing submandibular and cervical adenitis, the clinical condition improved although the fever remained unabated. This suggests that glomerulonephritis was unlikely to have been caused by a post-GABHS infection, and that other causes of infective AGN might have been involved. However, despite our patient not having any sore throat or skin lesions to suggest GABHS infection, his blood culture on admission grew *S. pneumoniae* (even though throat swab culture was negative) indicating that the organism was indeed the causative agent.

In most patients with post-infectious glomerulonephritis following pneumococcal pneumonia,^(1,2,4,5) respiratory symptoms were the first to appear, followed by renal manifestations. In our patient, however, renal involvement was the first manifestation and pneumonia with pleural effusion only developed later.

Similar to our patient, the elevation of serum ASOT accompanying glomerulonephritis was noted in three other studies of AGN in association with pneumococcal infection.^(4,5,8) ASOT is normally known to be associated with group A streptococci infection.^(1,4) Immunofluorescence studies have also shown that elevated serum titre of ASOT is associated with the deposition of pneumococcal polysaccharides in the glomeruli.⁽⁴⁾

Studies have suggested that post-streptococcal glomerulonephritis is mediated by the deposition of circulating immune complexes or causative antigens/pathogens in the glomeruli.^(4,6) According to immunofluorescence studies, pneumococcal polysaccharide bound to the mesangium and glomerular basement membrane may activate the classical and/or alternative complement pathways leading to the deposition of such compounds and the subsequent development of reversible glomerulonephritis.^(4,6) The reduced C3 and/or C4 levels, as reported in these patients, are compatible with classical and/or alternative complement activation.

To summarise, we herein presented the case of a four-year-old boy who developed AGN following pneumococcal bacteraemia and submandibular lymphadenitis, and highlighted the unusual presentation of *S. pneumoniae* complicated with AGN. To our knowledge, this is the first report of a patient in whom renal manifestations preceded respiratory symptoms in pneumococcal AGN. *S. pneumoniae* should be considered in the differential diagnosis of children presenting with febrile AGN with and without respiratory involvement.

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