CASE REPORT

Acute glomerulonephritis secondary to *Streptococcus anginosus*

Satish Maharaj,[1] Karan Seegobin,[2] Stephen Chrzanowski,[2] Simone Chang[3]

[1]Internal Medicine, University of Florida College of Medicine, Jacksonville, Florida, USA
[2]College of Medicine, University of Florida, Gainesville, Florida, USA
[3]Hotz Children's Hospital, Jackson Health Sysrem, Miami, Florida, USA

Correspondence to
Dr Satish Maharaj, satishsmaharaj@gmail.com

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SUMMARY

Streptococcus anginosus is a clinically important pathogen that is emerging globally but remains poorly investigated. Here, we report the first case of acute glomerulonephritis resulting from infection with *S. anginosus*. Glomerulonephritis is typically caused by *S. pyogenes* and reports secondary to other strains including *S. zooepidemicus* and *S. constellatus* exist. Infection with *S. anginosus* in this patient was associated with acute nephritis (haematuria, oedema and hypertension), nephrotic syndrome and progressive azotemia. There was activation of the complement system. The presence of low C1q and elevated anti-C1q binding complexes points to a potential pathogenic role. Testing for streptococcal antigens was strongly positive. Emerging nephritogenic strains of *S. anginosus* present a significant health concern for both developed and developing countries.

BACKGROUND

Streptococcus anginosus is a clinically important pathogen that is emerging globally but remains poorly investigated. Here, we report the first case of acute glomerulonephritis resulting from infection with *S. anginosus*. Acute glomerulonephritis is well known to be induced by nephritogenic strains of group A beta-haemolytic streptococcus, typically caused by *S. pyogenes*, but reports secondary to other strains including *S. zooepidemicus* and *S. constellatus* exist. Overt glomerulonephritis in the setting of infection with only *S. anginosus* has never been reported before, to the best of our knowledge.

CASE PRESENTATION

A 55-year-old African-American woman presented to the emergency room with a chief complaint of haemoptysis. Physical examination revealed an ill-appearing patient with poor dentition, decreased air entry, dullness to percussion and crackles in the right lung fields, and costovertebral tenderness in the left flank. Initial laboratory testing was significant for a leucocytosis, elevated creatinine and elevated C reactive protein (table 1). Urinalysis, obtained prior to medication administration, revealed microscopic haematuria, red blood cell casts and leucocyturia. Thoracic CT imaging revealed a right upper lobe necrotising pneumonia (figure 1). Intravenous vancomycin, piperacillin–tazobactam and clindamycin were promptly started. Testing for eosinophiluria was negative. Blood cultures were drawn, and *S. anginosus* was initially identified using the Luminex Verigene Gram-positive blood culture assay. This molecular assay was performed directly on the positive blood cultures. The subsequent isolated colonies from the blood cultures as well as the fluid culture were identified using conventional methods—catalase, colony size, colony odour, haemolysis and PYR (pyrrolidonyl arylamidase) testing. Testing for coinfection with HIV and hepatitis B and C were negative.

Her abdominal pain persisted and serial imaging eventually revealed abdominal wall necrotising fasciitis with bullae in the affected area by day 5 (figure 2). Surgery debrided the wound, and a chest tube was administered for drainage. Intraoperative samples were collected, also growing *S. anginosus*. Five days after admission, she complained of dark 'cola-coloured' urine (figure 3) and developed anasarca. Hypertension became uncontrolled and renal function declined, though there was preserved urine output. Serum testing revealed markedly decreased CH50 and C3, normal C2 and C4, and increased C1q binding complexes (table 1). Additionally, there were elevated titres of antibodies to extracellular streptococcal products (anti-streptolysin-O (ASO) and anti-DNAse B; table 1). With clinical and laboratory evidence of acute nephritis and confirmation of antecedent streptococcal infection, the diagnosis of poststreptococcal glomerulonephritis (PSGN) was made using the Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines.[1] A renal biopsy was considered, but given strong evidence of PSGN, we abided by KDIGO recommendations to not obtain a renal biopsy. Additionally, the presence of abdominal wall infection was a relative contraindication.

The patient was managed conservatively with antibiotic therapy, blood pressure control, diuresis and careful fluid management. Broad-spectrum antibiotics (vancomycin, piperacillin–tazobactam and clindamycin) were downgraded to ceftriaxone and metronidazole when the *S. anginosus* strain was identified as pansusceptible (testing done for ceftriaxone, clindamycin, penicillin and vancomycin). Anaerobic coverage was maintained empirically with the nature of infections. There was clinical and biochemical improvement with good recovery. The patient was discharged to a nursing facility in stable condition and followed in clinic after.

INVESTIGATIONS

Figure 4 shows the trends in C3 complement and proteinuria measured by spot protein:creatinine

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Table 1 Laboratory investigations on admission

Test	Result (normal range)
Leucocyte count	19.51 (4.5–11×10^9/L)
Procalcitonin	23.17 (<0.15 ng/mL)
C reactive protein	86.5 (0.0–5.0 mg/L)
BUN	22 (2–22 mg/fL)
Creatinine	0.55 (0.55–0.95 mg/dL)
Urinalysis	>180 wbc, >180 rbc, >100 protein, 0–10 eosinophils/HPF
Urine protein:creatinine (spot, early morning void)	1.37 (<0.16 mg/mg)
C1q binding complexes	5.5 (<4.4 µg Eq/mL)
C1Q	11.6 (11.8–28.4 mg/dL)
C2	3.2 (1.6–4.0 mg/dL)
C3	42 (90–180 mg/dL)
C4	12 (10–40 mg/dL)
CH50	12 (42–60 U/mL)
Anti-streptolysin O titre	1944 (<200 IU/mL)
Anti-DNAse B antibodies	8850 (0–120 U/mL)

Blood urea nitrogen (BUN); White blood cells (wbc); Red blood cells (rbc); High power field (hpf).

ratio on an early morning void sample. The C3 complement levels decreased to a nadir then uptrended slowly, while the proteinuria increased until day 8 and then returned to baseline. On discharge, the C3 complement level had almost normalised at 82 mg/dL.

OUTCOME AND FOLLOW-UP

There was clinical and biochemical improvement with good recovery. The patient was discharged to a nursing facility in stable condition and followed in clinic after. At follow-up 3 months later, the patient had good recovery with normal renal function and the C3 complement level had normalised (132 mg/dL).

DISCUSSION

Of the streptococcal species, *S. anginosus* is the least investigated of the streptococci. To many physicians, *S. anginosus* remains

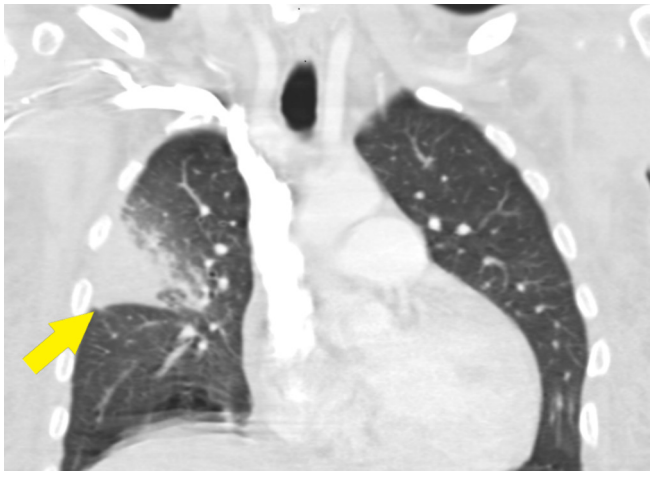

Figure 1 CT chest with intravenous contrast. There is dense consolidation and enhancement of the right upper lobe, which causes mass effect and bowing of the minor fissure (arrow). There are central areas of low attenuation suggesting necrosis or intrapulmonary abscess, and there is surrounding ground-glass opacity involving the majority of the inferior lateral right upper lobe.

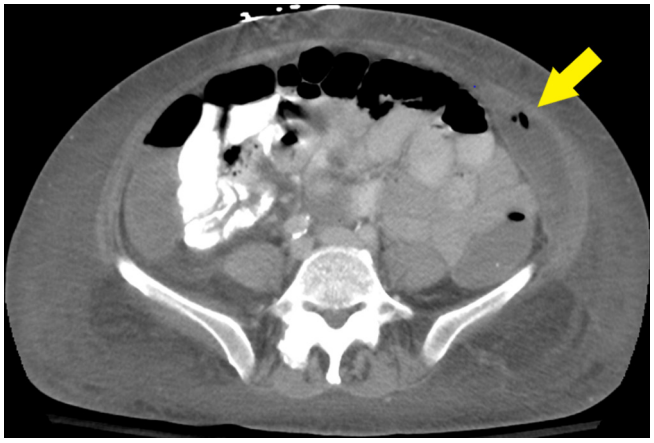

Figure 2 CT abdomen with intravenous contrast. There is an expanding collection in the left extraperitoneal space involving the left transversus abdominis and oblique musculature with internal foci of gas (arrow).

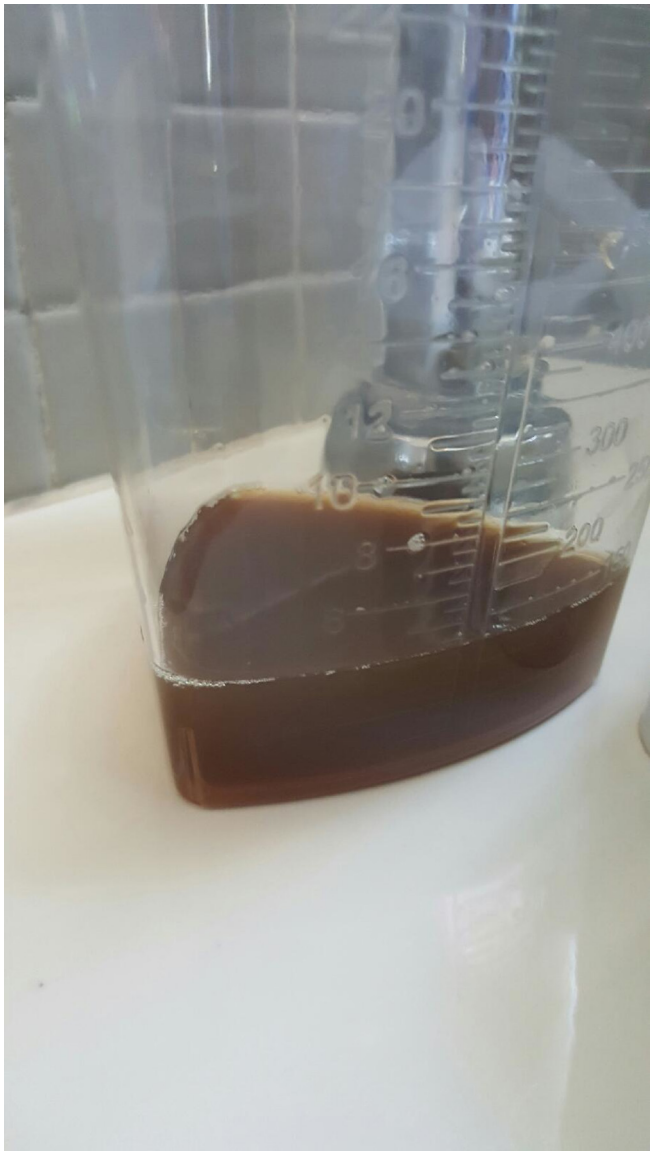

Figure 3 Urine sample: tea-coloured urine was the first symptom prompting investigation.

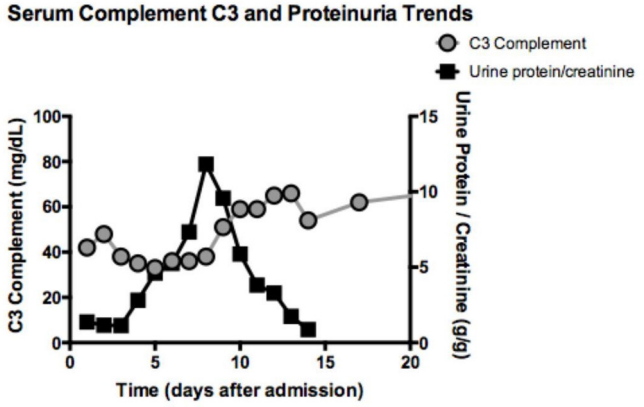

Figure 4 Serum complement C3 and proteinuria trends.

shrouded in medical mystery with confusion regarding its classification hampering detailed investigation and diagnosis of infections.[2] *S. pyogenes* is well known as 'group A beta-hemolytic streptococcus' (GAS) because it demonstrates haemolysis on blood agar and carbohydrate 'group' antigens. However, this dichotomous classification is limited for *S. anginosus*, which can be α-non-haemolytic, β-non-haemolytic or non-haemolytic, and express A, C, G, or F, or no Lancefield antigen.[3] *S. anginosus* has also been considered a viridans streptococci and associated with Lancefield group F.[4] This demonstrates the confusion regarding *S. anginosus*. In this case, the *S. anginosus* was typed as Lancefield group A.

Further research to redefine and classify *S. anginosus* is ongoing using chromogenicity and multilocus sequence analysis,[2 5–7] but a paucity of information still exists regarding *S. anginosus* and their role in human infection. *S. anginosus* can be pathogenic and is notorious for causing abscesses, particularly in the lungs and abdomen. A 2-year surveillance study by the CDC recently revealed that significant associations for *S. anginosus* infection included age (<65 years), diabetes mellitus and patients admitted from home.[4] Previously known clinical syndromes resulting from *S. anginosus* infections include bacteraemia, abscess formation, pneumonia, intra-abdominal infection, osteomyelitis and less commonly endocarditis, necrotising fasciitis and streptococcal toxic shock syndrome.[4] It remains unclear what clinical differences, if any, exist between α-non-haemolytic, β-non-haemolytic and non-haemolytic *S. anginosus* group isolates and what the true burden of infection is for cases involving *S. anginosus*.

A review of the literature documents cases and outbreaks of glomerulonephritis globally from *S. pneumoniae*, *S. zooepidemicus* and *S. constellatus* dating back to the 1960s.[8 9] More recently, animal models have also suggested glomerulonephritis is possible from non-GAS strains.[10] This case suggests that *S. anginosus* may harbour or induce nephritogenic antigens. In 2005, Almroth *et al*[11] examined an outbreak of acute glomerulonephritis among four families in Sweden that coincided with the spread of *S. constellatus*. There was also infection with *S. anginosus*, though this strain was not directly implicated. Kidney biopsies revealed an acute diffuse proliferative glomerulonephritis compatible with acute poststreptococcal nephritis and microbiological analysis of renal tissue revealed both *S. pyogenes* and *S. constellatus*.

Glomerulonephritis associated with *S. zooepidemicus* has also been previously reported.[12] In 1998, there was a large outbreak (134 patients) of acute glomerulonephritis in Brazil, which was investigated by the CDC. Lancefield group C *S. zooepidemicus* was identified as the causative organism and linked to the consumption of cheese produced from unpasteurised milk.[13] There were four mortalities in the acute phase and five patients (3.7%) required chronic dialysis. Follow-up was continued for 10 years and demonstrated morbidity with patients developing hypertension, reduced renal function and increased microalbuminuria, which peaked within the first 2 years with subsequent stabilisation.[14 15] A unique feature of this case is that the patient had two streptococcal infections. In the strictest sense, we are unable to say if the necrotising fasciitis was secondary or second to be identified. In a search of MEDLINE/PubMed, we were unable to find any cases of glomerulonephritis with necrotising fasciitis.

The glomerulonephritis in poststreptococcal disease is thought to be mediated by intraglomerular immune complex formation induced by deposition of nephritogenic streptococcal antigens. In situ formation is augmented by circulating immune complexes, which further activate the complement pathway locally. Therefore, we wondered if *S. anginosus* strains have been described as antigenically similar to *S. pyogenes*. A review of the literature revealed that *S. anginosus* is known to be phenotypically diverse; whole-genome comparative analysis has demonstrated significant variation in genomic size with multiple rearrangements, insertions and deletions.[16] A primary virulence factor of *S. anginosus* includes homologues of streptolysin S, a haemolytic exotoxin described in *S. pyogenes*.[17 18] Although research is limited, streptolysin O and DNase B antibodies have not previously been associated with *S. anginosus*. However, in the light of our patient having a markedly elevated anti-streptolysin O titre, we hypothesise that streptolysin O and DNAse B may be expressed, potentially as virulence factors, in some *S. anginosus* strains. This is an exciting observation that we think deserves further research, which has been started.[2]

Recently, Babbar *et al*[2] examined α-haemolytic and β-haemolytic *S. anginosus* isolates from India and Germany. Complementary PCR-based screening for *S. pyogenes* virulence factors revealed a subgroup of *S. anginosus* that harbours superantigen and extracellular DNAse coding genes identical to corresponding genes of *S. pyogenes*. Interestingly, this patient also had elevated levels of C1q binding complexes with decreased serum C1q. Antibodies against complement C1q (anti-C1q) strongly have also been implicated in other cases of nephritis.[19 20] These findings deserve further investigation.

Learning points

- Infection with *Streptococcus anginosus* in this patient was associated with acute nephritis (haematuria, oedema and hypertension), nephrotic syndrome and progressive azotemia.
- There was activation of the complement system with decreased complement C3 and C1q and elevated anti-C1q binding complexes.
- Testing for streptococcal antigens was strongly positive (streptolysin O, DNAse B), and this deserves further investigation.
- Emerging nephritogenic strains of *S. anginosus* present a significant health concern for both developed and developing countries.

Contributors SM and KS conceived the idea for the study. SM, KS and SC were directly involved in patient care. SM and SC collected the data and wrote the case report. KS and SC performed the literature review and prepared the supplementary material. All authors contributed to the discussion and approved the final draft of the manuscript.

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Patient consent Obtained.

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