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Case Report: Concurrent Rheumatic Fever and Acute Post-Streptococcal Glomerulonephritis in a High-Burden Setting

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Abstract. We report a case of acute rheumatic fever with severe pancarditis occurring simultaneously with probable acute post-streptococcal glomerulonephritis in a previously well, Australian Aboriginal, 29-year-old male. These autoimmune streptococcal sequelae are usually considered pathogenetically distinct, and concurrence has not previously been reported from this high-burden setting. We hypothesize that a single type of infecting group A *Streptococcus* (Strep A) triggered both autoimmune sequelae. Salient features included mitral and aortic regurgitation that worsened during the acute illness, painful pericarditis, and high troponin; severe acute kidney injury with oliguria, hematuria, and macroalbuminuria; reduced complement (C3); and elevated streptococcal serology. The case highlights important diagnostic and management challenges. It also illustrates the serious morbidity impact of the complications of Strep A.

CASE REPORT

A 29-year-old Australian Aboriginal man from a remote community presented with a 4-day fever, migratory large-joint polyarthritis, productive cough, and recent sore throat. He was treated in the community for pneumonia with procaine penicillin IMI 1.5 g daily according to local guidelines.[1] He had no relevant past medical history.

On arrival at the hospital, he posed a diagnostic dilemma. He had a fever, 39.9°C; respiratory rate, 40 breaths/minute; sinus tachycardia, 124 beats/minute; normal blood pressure (with no documented hypotension); normal oxygen saturation, and no edema. He had a marked antalgic gait and mild left elbow and bilateral knee effusions with warmth and tenderness. Right basal inspiratory crepitations were present. He had no audible murmur initially, and no pyoderma, rash, or evidence of pharyngitis.

Investigations showed raised white cell count, 30×10^9/L (reference range [RR], 4.0–11.0 $\times 10^9$/L); neutrophils, 25×10^9/L (RR neutrophils 2.0–7.5 $\times 10^9$/L); C-reactive protein, 334 mg/L (RR 0.0–5.0 mg/L); and erythrocyte sedimentation rate, 75 mm/hour (RR 1–15 mm/hour). He had acute renal injury: urea, 11.5 mmol/L (RR 3.0–7.5 mmol/L); creatinine, 399 μmol/L (RR 60–110 mmol/L) with macroalbuminuria (urine albumin: creatinine ratio, 949 g/mol: RR < 2.5 g/mol), and an active urinary sediment containing white (> 100×10^6/L: RR < 10×10^6/L) and red blood cells (> 100×10^6/L: RR < 10×10^6/L) without casts, eosinophils, or bacterial growth. Complement levels were initially normal: C3, 1.00 g/L (RR 0.86–1.84 g/L) and C4, 0.26 g/L (RR 0.20–0.59 g/L). He had markedly elevated troponin-I (high-sensitivity troponin-I 737 [RR < 16 ng/L]). electrocardiograph (ECG) demonstrated sinus tachycardia with a normal PR interval of 192 milliseconds (RR < 200 milliseconds) and no features of infarction. Chest X-ray revealed mild enlargement of the cardiomediastinal silhouette. He was initiated in the emergency department on intravenous meropenem and vancomycin for community-acquired sepsis in the tropical monsoon season.

A transthoracic echocardiogram was significant for a mitral valve that was thickened and "rheumatic" in appearance, with moderate eccentric mitral incompetence and mild aortic regurgitation. Provisional diagnoses of acute rheumatic fever (ARF), acute kidney injury of uncertain etiology, and bronchitis were made. High-dose aspirin (50 mg/kg) for the management of ARF joint symptoms was relatively contraindicated, given the renal failure, and was thus withheld until normalization of his creatinine. Intravenous daily ceftriaxone 2 g and renally-adjusted flucloxacillin 1 g 8-hourly replaced the initial antibiotic regimen to cover for potential infective endocarditis.

Over the next 3 days, he developed chest pain consistent with pericarditis, an audible murmur consistent with mitral regurgitation, and atrial fibrillation. Trans-esophageal echocardiogram showed progression to severe mitral regurgitation and moderate aortic regurgitation. No vegetations were visualized, and thus antibiotics were ceased. Troponin-I rose to 959 ng/L and renal function deteriorated to oliguric renal failure (maximum urea 25 mmol/L and creatinine 698 μmol/L). A mild decrease in C3 was observed to 0.82 g/L. Nadir serum albumin was 28 g/L (RR 39–50 g/L) and the lipid profile was normal. Renal ultrasonography was unremarkable.

He was commenced on prednisolone 1 mg/kg daily on day 3 of admission. Chest pain and arthritis improved and creatinine normalized within 12 days. Renal biopsy was not undertaken, given the improvement. Chest pain recurred on tapering of prednisolone after 14 days; there was good symptomatic response to a dose increase with a slower wean.

Autoimmune screening (antinuclear antibodies, extractable nuclear antigen antibodies, antineutrophil cytoplasmic antibodies, double-stranded DNA, and antiphospholipid antibodies) was negative. He was immune to hepatitis B and negative for hepatitis C and HIV. Glycated hemoglobin was normal. Blood, sputum, and throat cultures, and urine nucleic acid tests for *Trichomonas*, *Chlamydia*, and *Neisseria* were negative. A rise in streptococcal serology occurred over a 12-day period: antistreptolysin O increased from 426 to 750 units (upper limit of normal [ULN] for his age, 177 units) and anti-DNAseB increased from 800 to 1,200 units (ULN, 390 units). This did not constitute a 2-fold rise but was consistent with recent streptococcal infection.[2]

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The constellation of carditis, polyarthritis, fever, raised inflammatory markers, and evidence of recent group A *Streptococcus* (Strep A) infection confirmed a definite diagnosis of ARF.[3,4] The presence of hematuria, proteinuria, and oliguria with reduced C3 with recent Strep A infection was supportive of probable acute post-streptococcal glomerulonephritis (APSGN). Diagnostic guidelines require a consistent renal biopsy or a clinically compatible illness with two of hematuria, hypertension, and facial or peripheral edema, plus laboratory evidence (hematuria, reduced C3, and evidence of streptococcal infection).[5] He had one clinical criterion and supportive laboratory criteria. His household contacts received benzathine benzylpenicillin-G in accordance with local guidelines for the public health response to APSGN.[5]

Serial echocardiograms showed evolution in valvular changes. He required mechanical aortic and mitral valve replacements 7 months later, after attention to dental hygiene which necessitated dental extractions. At 2-year follow-up, he remained highly adherent to benzathine benzylpenicillin-G 900 mg intramuscular injections, which he received on average every 24 days, and warfarin. No further episodes of ARF or APSGN were documented. However, he did develop bacteremia and likely prosthetic valve endocarditis with *Aggregatibacter actinomycetemcomitans* 22 months later. The penicillin minimum inhibitory concentration was 2 mg/L, well above that achievable with benzathine benzylpenicillin-G. Notably, throughout that admission, renal function was entirely normal. Antistreptolysin O at that time was not elevated at 78 units.

DISCUSSION

To our knowledge, this is the first reported case of an Australian Indigenous adult with ARF-associated pancarditis and probable APSGN. Despite having world-leading rates of ARF[6] and APSGN[7] in northern Australia, concurrence of these conditions has not been seen locally. We propose that concurrence is uncommon because of the distinct pathogeneses of ARF and APSGN; but in this case, Strep A infection precipitated distinct, concurrent pathological immune responses triggering both processes.

The pathogeneses of ARF and APSGN are thought to differ with regard to host immune responses and the Strep A types that elicit the respective autoimmune sequelae. The immunological pathogenesis of ARF remains poorly understood, but research is underway to address this.[8] The prevailing hypothesis is molecular mimicry: the Strep A M protein and/or carbohydrate molecules have antigen epitopes resembling those in target human cells, thus triggering autoantibody production.[9,10] An alternative hypothesis is that autoimmunity is triggered because Strep A infection disrupts collagen in the extracellular matrix and exposes cryptic epitopes.[11] The pathogenesis of APSGN is better understood. It is associated with binding of streptococcal glyceraldehye-3-phosphate dehydrogenase and SpeB to glomeruli.[9,12] This induces an inflammatory reaction, causing glomerular basement membrane injury and deposition of immune complexes.[13]

Acute post-streptococcal glomerulonephritis tends to occur in cyclical outbreaks. Certain Strep A M types (e.g., *emm*55.0) have been identified locally as "nephritogenic".[7] Because ARF tends to be sporadic, identifying "rheumatogenic" strains is more difficult. Studies indicate that types associated with ARF in the southern hemisphere tend to differ from those classically recognized in past northern studies,[14] and that a broad array of types are likely to trigger ARF.[15]

The diagnosis of pancarditis was based on the constellation of evolving valvulitis, pain consistent with pericarditis, and high troponin consistent with myocarditis. Rheumatic pancarditis is rare.[3,16] A small number of old case reports exist, mostly in children.[17–23] The prevalence of renal injury in the context of ARF is unknown but is uncommon, especially in adults and in Australia.[6,7,24] The concurrence of ARF and APSGN has been observed previously in other settings.[12,24–35] Pancarditis associated with APSGN has only previously been reported in two children.[20,29]

Acute post-streptococcal glomerulonephritis was considered the likeliest explanation for the renal injury. An important limitation of this report is the absence of renal tissue to provide a more definitive explanation for the renal injury. Although a biopsy was planned, the creatinine level had already started to improve by day 4 and, hence, this was not believed to be clinically necessary. Also, although C3 level was below the RR, the reduction was modest. We note that local[5] and international[36] data indicate that a low C3 is not mandated in definite diagnoses of APSGN. There was no evidence of hemodynamic instability or epithelial cells and granular casts in the urinary sediment to suggest acute tubular necrosis.[37] A potential differential diagnosis was acute interstitial nephritis (AIN) secondary to infection or initial receipt of antibiotics in the community. However, onset was rapid, a relationship to antibiotics was not evident, eosinophilia was not present, and although an infective component (bronchitis) of the presentation was considered likely, this was not severe. In addition, AIN is usually associated with polyuria and only mild proteinuria.[38] Other differentials were also sought (e.g., diabetes and vasculitis) and excluded. As noted, his renal function was normal 22 months later at representation with sepsis due to endocarditis.

Corticosteroids were prescribed because of the severity of carditis. Guidelines support their use in this context (1–2 mg/kg/day), but acknowledge a lack of evidence,[3] including from systematic review.[39] In the few reported ARF cases with concurrent APSGN, recovery of renal injury has followed corticosteroid initiation.[12,13,26] However, APSGN is usually self-limiting, with resolution typically commencing within 1 week of presentation; hence, any role for steroids is not proven.[40]

It was unclear whether this presentation was a first or recurrent ARF episode. The echocardiographic images were reviewed with reference to the World Heart Federation criteria for diagnosis of rheumatic heart disease (RHD).[41] Given that the initial echocardiogram already revealed deformed valve leaflets, it is possible that subclinical RHD was preexisting. This is consistent with local data, indicating that 70–80% of RHD diagnoses are made in people without previously recognized ARF, or soon after first ARF, because subtle ARF is readily missed. Local awareness-raising campaigns are seeking to overcome this problem.

The ongoing high rates of ARF and RHD among Aboriginal people in remote northern Australia are now mobilizing increasing attention, and a strategy for RHD elimination is being developed. The unfortunate later complication of infective endocarditis in this case, despite high adherence to recommended treatment, highlights the heavy burden suffered by

young people living with RHD and is illustrative of the need to prevent this condition through primary preventive strategies.

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