Case Report

Non-rheumatic streptococcal myocarditis – warm hands, warm heart
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Acute myopericarditis in the developed world is ascribed predominantly to viral infections. Enteroviruses and adenoviruses are commonly implicated but are not routinely tested for, as the condition is self-limiting and has a good prognosis. However, we recently encountered two cases of acute myopericarditis associated with concomitant Streptococcus pyogenes [group A Streptococcus (GAS)] pharyngotonsillitis. A microbiological aetiology was pursued because of the severity of the upper respiratory tract infection and associated systemic illness rather than to explain the myopericarditis per se. We report these two cases and review the literature of this potentially under-recognized condition. In the absence of features of rheumatic fever, we hypothesize a toxin-mediated process as opposed to an immune-mediated one. We suggest that perhaps all patients with myopericarditis be assessed for GAS pharyngitis.

Case reports

Case 1
A 29-year-old male was brought to our emergency department with left-sided chest pain and high fevers. He had developed a sore throat 3 days prior to admission which progressed to odynophagia and mild trismus at the time of admission. Urgent ENT consultation confirmed a peritonsillar abscess, which was treated with incision and drainage under local anaesthesia. Simultaneous investigation of his chest symptoms revealed widespread ‘saddle-shaped’ ST elevation and a raised serum cardiac troponin I (cTnI) (peak level 25 ng l−1). An echocardiogram revealed mild segmental systolic dysfunction and regional wall motion abnormalities (Table 1). The temporal pattern of cTnI levels was not monophasic and the ECG evolution was not typical of myocardial infarction. Coronary artery disease was a possibility, which prompted additional investigations of cardiac magnetic resonance imaging (MRI) and left heart catheterization. MRI showed moderate systolic dysfunction left ventricular ejection fraction 39% which was segmental but no obstructive coronary artery disease was found on coronary angiogram. Abnormal MRI was consistent with diffuse myopericarditis, with oedema and late gadolinium enhancement in subepicardial and intramural regions (Fig. 1). Left heart catheterization revealed abnormal haemodynamics of relative hypotension with elevated left ventricular end-diastolic pressure. A diagnosis of myopericarditis was made and the patient was admitted with cardiac monitoring.

Intravenous penicillin was commenced for peritonsillar abscess, which shortly grew group A Streptococcus (GAS). Streptococcal serology done soon after admission was negative. The patient remained febrile, appeared flushed with warm bounding peripheries but was haemodynamically robust (heart rate of 90–100 b.p.m.; blood pressure of 130/70 mmHg; mean arterial pressure of 90 mmHg). Minimal improvement of his pharyngeal symptoms prompted a repeat incision and drainage, plus the addition of intravenous lincomycin for presumed anaerobic bacterial infections potentially resistant to penicillin. He made a gradual recovery over 5 days and lincomycin was ceased when no other pathogens were isolated. He was discharged from hospital after a week and completed a 1-week course of oral amoxicillin at home. On follow-up, the patient was well, and an echocardiogram performed 13 days post-admission revealed normalized parameters (Table 1). On review at 3 months, the patient was asymptomatic with normal echocardiogram parameters.

Case 2
An 18-year-old, previously healthy, Caucasian male developed a sore throat with fevers. He was empirically started on oral amoxicillin for a clinical diagnosis of GAS pharyngitis by his general practitioner. Three days into his illness, he developed precordial chest pain that was positional and he continued to have fevers. On day 6 of his illness, he was transferred to our tertiary centre for persistent chest pain thought to be pericarditic. He was noted to be febrile to 39 °C and appeared flushed. Except for mild tachycardia of 100–110 b.p.m., his haemodynamic parameters were satisfactory (blood pressure of 110/...
65 mmHg; mean arterial pressure of 80 mmHg). ECG revealed widespread ST elevation characteristic of peri-carditis, and a raised serum cTnI (peak level 7.7 ng l$^{-1}$) confirmed myocarditis. An echocardiogram revealed normal mild systolic dysfunction, normal valvular physiology and minimal pericardial fluid (Table 1). His symptoms were thought to be predominantly pericarditic and he was commenced on aspirin. The initial clinical suspicion of GAS infection prompted a throat swab, which, on culture, revealed GAS. The patient was commenced on intravenous penicillin due to ongoing fevers. The patient made an uneventful recovery allowing de-escalation to oral amoxicillin after a few days. He completed a total of 2 weeks of antibiotic treatment with no untoward effects. Anti-streptolysin O titres returned weakly positive at 230 U ml$^{-1}$ (reference range, 200 U ml$^{-1}$), 1 week after the onset of pharyngitis. A follow-up echocardiogram performed 8 days post-admission revealed early recovery of myocardial function (Table 1).

### Discussion

The question of rheumatic fever was predictably raised in both our patients. However, neither of them had any of the other features that met the revised Jones criteria for acute rheumatic fever (Dajani et al., 1992). The pretest probability of acute rheumatic fever was low because, in Australia, it is encountered almost exclusively in non-urban Aboriginal and Torres Strait Islander people (Carapetis et al., 2007). Both our patients were Caucasian males from Brisbane.

The typical latency between GAS pharyngitis and carditis in acute rheumatic fever was notably absent in our cases. The synchronous nature of the active infective process with carditis, rather than delayed response, did not support primary rheumatic fever. A non-immune-mediated process was also supported by the lack of streptococcal antibodies in case 2, where they were measured shortly after the onset of clinical carditis.

The other well-described condition is that of myocarditis associated with invasive streptococcal infection or toxic-shock syndrome. This condition is typically fulminant with a rapid onset and thus unlikely to be the case in our patients (Stevens, 1995). Moreover, the ‘flushed’ appearance in both our patients was a sign of peripheral vasodilatation and did not progress to desquamation as would be noted in rashes associated with some toxic-shock syndromes. The inability to fully elucidate the pathogenic mechanism in these two cases has made apparent a gap in our understanding and therefore management of this condition.

We reviewed the literature looking for articles referring to ‘non-rheumatic’ streptococcal myocarditis and found seven papers that have clinical similarities to the cases described in this report. The most recent report of eight young individuals in 2010 documented the biochemical, ECG, echocardiographic and cardiac MRI findings of this condition (Mokabberi et al., 2010). Albeit a small series, the imaging studies in this paper suggest that the myocarditis resolved with antibiotic therapy, although in the absence of a ‘negative control’, the role of antibiotics is not certain. It must be noted that all the patients developed myocarditis while on antibiotics for pharyngitis and received additional treatment with non-steroidal anti-inflammatory

### Table 1. Echocardiogram parameters on admission and at follow-up

<table>
<thead>
<tr>
<th>Case</th>
<th>Interval (days)</th>
<th>LV size</th>
<th>LVEF (%)</th>
<th>RWMA</th>
<th>RV (size/systolic function)</th>
<th>Valvulitis</th>
<th>Valvulopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>On admission</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Normal</td>
<td>48</td>
<td>Apical/apical-inferior akinesis</td>
<td>Normal</td>
<td>Nil</td>
<td>Grade 0–1/4 MR</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Normal</td>
<td>52</td>
<td>Apical hypokinesis</td>
<td>Normal</td>
<td>Nil</td>
<td>Grade 1/4 AR</td>
<td></td>
</tr>
<tr>
<td>At follow-up</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>13</td>
<td>Normal</td>
<td>55–60</td>
<td>None</td>
<td>Normal</td>
<td>Nil</td>
<td>Trivial TR</td>
</tr>
<tr>
<td>2</td>
<td>8</td>
<td>Normal</td>
<td>68</td>
<td>None</td>
<td>Normal</td>
<td>Nil</td>
<td>Grade 1/4 AR</td>
</tr>
</tbody>
</table>

![Fig. 1. T2 weighted double inverse recovery sequence short axis projection demonstrating myocardial oedema (arrow).](image)
agents when diagnosed with carditis. Beta-blockers were employed in five out of the eight cases.

A series of four very similar cases in Israel were analysed to try and explain the pathogenesis. This bioinformatics study described similar peptide sequences between human cardiac Ca\(^{2+}\) ATPase and a GAS putative calcium-transporting ATPase. These authors postulated molecular mimicry and cross-reactivity as a pathogenic mechanism but rightly concluded that the finding of similar peptides in itself cannot prove cross-reactivity nor explain the pathogenesis (Malnick et al., 2010).

A case report and literature review in 1995 refers to ‘direct or indirect bacterial toxin action’ as the pathophysiology but the basis for this appears to be speculative (Gill et al., 1995). Interestingly, the most illuminating study as far as pathogenesis is concerned is probably the earliest one. In 1947, Gore and Saphir of the United States Army described 35 cases of fatal myocarditis that followed acute tonsillo-pharyngitis in a retrospective study (Gore & Saphir, 1947). Diphtheria was ruled out by clinical and bacteriological methods, as was direct streptococcal bacterial invasion, on myocardial histopathology done on autopsy. Streptococci were isolated from throat swabs from 12 patients; however, grouping or Lancefield typing was unavailable when these cases were initially recorded. Thus group A streptococcal tonsillitis as the aetiology of myocarditis, although conjectural, was very possible. The histopathological findings revealed focal to diffuse myocardial infiltration with predominantly mononuclear cells and areas of necrotic muscle fibres. These histological findings are similar to those described in diphtheritic myocarditis, which is a toxin-mediated process (Gore & Saphir, 1947). The more recent literature has focused on the clinical aspects, and some interesting commonalities are summarized in Table 2.

In summary, this condition appears to predominantly affect young males on \(\beta\)-lactam antibiotics for the treatment of tonsillitis or pharyngitis. The onset of chest pain was most often noted on day 3 of the upper airway infection. All of them made a good clinical recovery in the short-term. Both our patients seem to fit perfectly into this cohort and add to this body of literature.

Although the short-term prognosis seems to be good, only a longitudinal study would be able to answer the question of long-term outcome as far as myocardial disease is concerned. This would have implications in terms of the effects of a recurrence and therefore the role of prophylactic antibiotics. Furthermore, the role of \(\beta\)-lactam antibiotics in this scenario is intriguing. The three possible effects of \(\beta\)-lactam antibiotic treatment are: (1) helps hasten recovery by microbial eradication of GAS; (2) precipitates myocarditis by the release of pyrogenic toxins and cellular fragments as a consequence of bacterial cell-wall lysis; (3) has minimal effect on the disease process due to a large number of bacteria in stationary phase of growth, which are less susceptible to cell wall-acting agents. A

### Table 2. Publications describing cases of microbiologically proven GAS tonsillitis with associated non-rheumatic myocarditis

<table>
<thead>
<tr>
<th>Reference, location</th>
<th>Age (years)</th>
<th>Latency (days from onset of sore throat to onset of chest pain)</th>
<th>No. of male patients</th>
<th>No. of patients receiving (\beta)-lactam antibiotic at onset of myocarditis</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Karjalainen (1989), Finland</td>
<td>2</td>
<td>20–21</td>
<td>2</td>
<td>2</td>
<td>Complete recovery</td>
</tr>
<tr>
<td>Gill et al. (1995), USA</td>
<td>1</td>
<td>16</td>
<td>1</td>
<td>1</td>
<td>Complete recovery</td>
</tr>
<tr>
<td>Talmon et al. (2008), Israel</td>
<td>11</td>
<td>20–35</td>
<td>11</td>
<td>3 (mean)</td>
<td>Complete recovery</td>
</tr>
<tr>
<td>Mokabberi et al. (2010), USA</td>
<td>8</td>
<td>20–35</td>
<td>8</td>
<td>3–7 (mean)</td>
<td>Complete recovery</td>
</tr>
<tr>
<td>Malnick et al. (2010), Israel</td>
<td>4</td>
<td>29–32</td>
<td>4</td>
<td>4</td>
<td>Complete recovery</td>
</tr>
</tbody>
</table>
toxin-mediated inflammation could continue unabated in this scenario.

The dearth of information in this regard warrants further research. Twenty-six reported cases in more than two decades suggest under-recognition or under-reporting. This is fathomable as cardiac disease and its emergent management would take precedence over what is perceived to be a benign throat infection. Early recovery from myocarditis would also tend to limit the depth of investigation into its aetiology, as a significant number of cases of infectious myocarditis in the developed world are attributed to ‘self-limiting’ viral infections (Cooper, 2009). However, it would be presumptive to label this a ‘benign’ condition when inotropic support was required in some of the cases (Mokabberi et al., 2010). In the absence of a clear understanding of the pathophysiology, more research is needed, including longitudinal follow-up.

Toxin-mediated myocarditis is perhaps the most popular explanation for this condition (Gore & Saphir, 1947; Caraco et al., 1988; Karjalainen, 1989; Gill et al., 1995; Talmon et al., 2008) but needs further investigation. As the streptococcal isolate from case 2 was not available for typing, we typed the organism in case 1 and found it to be ‘emm101’ – not a known rheumatogenic strain. The role of lincosamides in addition to penicillin would be an attractive proposition if toxin production was proven. Lincosamides, which act on bacterial RNA to inhibit protein synthesis, might abort the duration of myocarditis by limiting toxigenicity (Stevens, 2003). However there are no precedents to recommend them as routine at this juncture.

Conclusions

The clinical association between streptococcal pharyngitis and non-rheumatic carditis has been described but remains ill-understood. We suggest that all myocarditis patients with a preceding upper airway infection have a throat swab for isolation and typing of GAS. Typing may help establish whether this is a strain-specific phenomenon and throw more light on its epidemiology. Sometimes the toxin-producing bacterial strains are found in clinically quiescent areas as colonizers. In fact, half the cases of streptococcal toxic shock syndrome have no clinically apparent portal of entry (Stevens, 1995). Thus, throat swabs looking for GAS could be considered in all cases of myocarditis. We suggest investigating a preceding upper airway infection, as it could be overlooked when matters of the heart take precedence.

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References


