Role of staphylococcal enterotoxin A in a fatal case of endocarditis

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A young female with no identifiable risk factors developed rapid, overwhelming Staphylococcus aureus endocarditis. Despite rapid sterilization of the blood and the mitral valve with optimal antimicrobials, she had persistent septic shock. In order to investigate this, the toxin-producing capacity of the infecting strain and the patient’s ability to produce antibodies were determined. The strain produced high levels of both α-toxin and staphylococcal enterotoxin A (SEA), whilst the patient responded with modestly high levels of antibodies to α-toxin and low-normal levels to SEA. The patient was most probably susceptible to the actions of SEA and developed a toxic-shock-syndrome-like disease that further aggravated her valvular dysfunction. This case illustrates that optimal antimicrobial therapy alone is not sufficient treatment in patients with persistent toxic shock and that there is a need to evaluate immunomodulatory strategies in such patients.

Case

A 21-year-old female presented to a peripheral clinic with 1 day of fever and otitis media, for which she received azithromycin. Three days later, she returned with high fever, systemic toxicity, dyspnoea and non-specific chest pain. Blood pressure was 80/60 mmHg, pulse 120, sinus tachycardia. Respiratory rate was 30 breaths min⁻¹. There was a grade 2/4 pansystolic murmur in the mitral area. Jugular venous pressure was not elevated. Bilateral fine crepitations were auscultated at both lung bases. Oder’s nodes and Janeway patches were present on her palms and soles. A right subconjunctival haemorrhage was present and a Roth spot was seen in the left fundus. There was no mucus membrane hyperaemia.

The peripheral white cell count was 14·1 × 10⁹ l⁻¹ (normal 4–11), predominantly neutrophils. The platelet count was 36 × 10⁹ l⁻¹ (normal 150–400), erythrocyte sedimentation rate 48 mm h⁻¹ (normal 2–14) and the complement regulatory protein (CRP) was 118 mg l⁻¹ (normal < 10). International normalized ratio (INR) was 1·8 (normal 0·8–1·2). The systemic vascular resistance fell from 1112 to 816 dynes s⁻¹ cm⁻⁵ l⁻¹ over the next 48 h. The respiratory failure worsened, with an FiO₂ requirement of 100 % and peak end-expiratory pressure (PEEP) of 13 cm H₂O to maintain an SaO₂ of 92 % and a PaO₂ of 64 mmHg. She was persistently pyrexial throughout, at between 38 and 38·5 °C. The cardiac index rose progressively from 4·6 to 5·7 l min⁻¹ m⁻² over the next 48 h. The systemic vascular resistance fell from 1112 to 816 dynes s⁻¹ cm⁻⁵ l⁻¹ over the same time. The central venous pressure was 11 mmHg and the pulmonary artery pressure was 19 mmHg. These haemodynamic parameters were suggestive of sepsis and non-cardiac pulmonary oedema. The arterial pH 1. D-dimers were 8000–4000 ng ml⁻¹ (normal 150–400), erythrocyte sedimentation rate 38·5 (normal 2–14) and the complement regulatory protein (CRP) was 118 mg l⁻¹ (normal < 10). International normalized ratio (INR) was 1·8 (normal 0·8–1·2). The systemic vascular resistance fell from 1112 to 816 dynes s⁻¹ cm⁻⁵ l⁻¹ over the next 48 h. The respiratory failure worsened, with an FiO₂ requirement of 100 % and peak end-expiratory pressure (PEEP) of 13 cm H₂O to maintain an SaO₂ of 92 % and a PaO₂ of 64 mmHg. She was persistently pyrexial throughout, at between 38 and 38·5 °C. The cardiac index rose progressively from 4·6 to 5·7 l min⁻¹ m⁻² over the next 48 h. The systemic vascular resistance fell from 1112 to 816 dynes s⁻¹ cm⁻⁵ l⁻¹ over the same time. The central venous pressure was 11 mmHg and the pulmonary artery pressure was 19 mmHg. These haemodynamic parameters were suggestive of sepsis and non-cardiac pulmonary oedema. The arterial pH

Abbreviations: PTSAg, pyogenic toxin superantigen; SEA, staphylococcal enterotoxin A; TSS, toxic-shock syndrome.
fell to 7.176, bicarbonate 15.5 mmol l$^{-1}$ and acid–base excess was –11.7 mmol l$^{-1}$. Repeated blood cultures on the second day were sterile.

Because of uncontrolled sepsis, she proceeded to emergency mitral valve replacement on the sixth admission day. The mitral valve anterior leaflets showed multiple vegetations and the chordae tendinae were ruptured. The mitral valve was excised and replaced with a St Jude bileaflet mechanical prosthesis. Despite maximum inotropic support and intra-aortic balloon pump assist, she could not be weaned off cardio-pulmonary bypass and died.

**Microbiological analysis**

A sample of serum taken within 48 h of admission (approx. 7 days into the illness and 3 days before death) was analysed for antibody titres to a variety of staphylococcal antigens as described previously (Kanclerski et al., 1996; Colque-Navarro et al., 2000). Toxin production of the infecting strain *in vitro* was determined.

The strain was shown to produce large quantities of β-toxin and staphylococcal enterotoxin A (SEA), but not toxic-shock-syndrome toxin 1 (TSST-1) (Table 1). The serum sample contained high levels of antibodies against β-toxin and low–normal levels against SEA.

**Discussion**

Staphylococcal endocarditis is a serious illness, particularly in left-sided, native-valve, community-acquired settings. The overall mortality is 22–34 % (Roder et al., 1999). One factor contributing to this mortality may be diagnostic delay due to the non-specific nature of the presenting features (Roder et al., 1999). An additional factor may be the relative insensitivity of transthoracic compared with transoesophageal echo in diagnosing staphylococcal endocarditis (Fowler et al., 1997), as illustrated by this case. The presence of several Oslerian features in this patient supported an early diagnosis of endocarditis and there was no delay in administering antimicrobial therapy. An age of over 60 years, late heart failure and neurological involvement are three identified poor prognostic factors in staphylococcal endocarditis (Roder et al., 1999; Watanakunakorn, 1994), but these were not present in this patient. Female gender, community-acquired infection and absent heart murmur have been identified as additional risk factors for death (Watanakunakorn, 1994).

Current antimicrobial therapy guidelines suggest that a combination of a beta lactam with an aminoglycoside (for the first 3–5 days) is the preferred regimen for non-penicillin-allergic, methicillin-sensitive *S. aureus* endocardi-

### Table 1. Toxin production of the infecting strain and antibody levels against *S. aureus* antigens in patient serum sample

<table>
<thead>
<tr>
<th>Antigen</th>
<th>Toxin production</th>
<th>Antibody levels</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Patient</td>
</tr>
<tr>
<td>Teichoic acid</td>
<td>NA</td>
<td>5180 (high)</td>
</tr>
<tr>
<td>Clumping factor</td>
<td>NA</td>
<td>165 (normal)</td>
</tr>
<tr>
<td>Fibrinogen-binding factor</td>
<td>NA</td>
<td>400 (normal)</td>
</tr>
<tr>
<td>β-Toxin</td>
<td>+++</td>
<td>736 (high)</td>
</tr>
<tr>
<td>TSST-1</td>
<td>–</td>
<td>40 (low)</td>
</tr>
<tr>
<td>Enterotoxin A (SEA)</td>
<td>+++</td>
<td>116 (normal)</td>
</tr>
<tr>
<td>Enterotoxin B</td>
<td>–</td>
<td>120 (low)</td>
</tr>
<tr>
<td>Enterotoxin C</td>
<td>–</td>
<td>448 (normal)</td>
</tr>
<tr>
<td>Enterotoxin D</td>
<td>–</td>
<td>61 (low)</td>
</tr>
<tr>
<td>Exfoliative toxin A</td>
<td>ND</td>
<td>&lt; 10 (low)</td>
</tr>
</tbody>
</table>

$^*$The upper 95th percentiles in a Swedish population were used as reference antibody levels. Data were taken from: $^a$, Colque-Navarro et al. (1998); $^b$, Colque-Navarro et al. (2000); $^c$, Kanclerski et al. (1996); $^d$, A. Serreli and others (unpublished results).

NA, Not applicable; ND, not done.
Surgery has a crucial role to play in the management of staphylococcal endocarditis. Long-term survival is significantly improved in patients treated medically/surgically compared with those treated medically alone (Cassada et al., 1999). Unfortunately, our patient progressed so rapidly that, by the third day, her condition was already critical and surgery would have had little to offer.

The infecting S. aureus strain was shown to produce high levels of both α-toxin and SEA. α-Toxin is a water soluble, 33 kDa single-chain polypeptide produced by a large proportion (85–96%) of clinically isolated S. aureus strains (Mölby, 1983). The toxin is considered to be haemolytic, dermonecrotic, neurotoxic and generally cytotoxic, and it exerts its toxic effect on a wide variety of mammalian cells through pore formation in the cell membrane. It is thought to be an important virulence factor in S. aureus infections, but its precise significance in human disease has not been fully elucidated. However, initially low antibody levels against α-toxin in patients have been shown to influence the severity of S. aureus septicemia, as 11 of 13 patients in one study with low levels of neutralizing antibodies in acute sera developed complicated septicemia (Colque-Navarro et al., 1998). The low–normal α-toxin antibody response in our patient is consistent with this. Due to the rapid demise of the patient, there was only one serum sample available for analysis of the antibody titres, and this limits the conclusions that can be drawn about the kinetics of the antibody response.

SEA has been linked to two distinct diseases: non-menstrual toxic shock syndrome (TSS), an acute and potentially fatal illness characterized by fever, hypotension, diffuse erythematous rash and involvement of at least three organ systems, and staphylococcal food poisoning. It is part of a family of related exotoxins secreted by either S. aureus or Streptococcus pyogenes, known as pyrogenic toxin superantigens (PTSAgs), whose most distinguishing property is their superantigenicity, i.e. the capacity to induce a disorderly, polyclonal expansion of certain T-cell subpopulations. This results in production of pathological levels of proinflammatory cytokines that contribute to severe pathology, primarily through toxic effects on the vascular endothelium (Dinges et al., 2000). Furthermore, the staphylococcal enterotoxins are potent emetic agents. Even though the symptoms displayed by our patient did not comply fully with the clinical case definition for TSS, there are several reasons to suspect that systemic effects caused by the toxins produced by the infecting strain contributed significantly to the fatal outcome in this case. Fever persistence, absence of important mortality predictive factors, presumed previously normal valves, progressive shock and multiorgan involvement and haemodynamic parameters suggestive of uncontrolled sepsis, despite rapid sterilization of blood cultures, suggests that staphylococcal toxins were at least as important as valvular dysfunction in the terminal events.

Menstrual TSS, which generally has its onset within 48 h of menstruation, is exclusively caused by colonization of the vaginal/cervical mucosa by TSST-1-producing S. aureus, since TSST-1 has the unique ability to cross mucosal barriers (Dinges et al., 2000). Non-menstrual TSS is the result of an S. aureus infection elsewhere in the body. Sixty per cent of cases are reported to be caused by TSST-1-producing strains, and the remaining cases are attributed to enterotoxin-producing strains, primarily SEB, but also other staphylococcal enterotoxins, especially SEA and SEC (Monday & Bohach, 1999). It is believed that a prerequisite for the disease to occur is low levels of antibodies to the respective toxins. Some patients seem unable to mount an antibody response to staphylococcal superantigens and they are thus prone to recurring TSS (Dinges et al., 2000).

The presence of SEA supports the role of this toxin in our patient. The low–normal antibody response to SEA, however, suggests either that there was a failure to mount a sufficient antibody response or that the staphylococcal disease was so rapid in progression that a more timely and avid antibody response could not be elicited, assumptions supported by the generally low titres against the other PTSAgs measured (apart from SEC).

It is therefore a moot point whether timely administration of intravenous immunoglobulin (IVIG) might have influenced the course of the disease in our patient. Evidence is mounting that IVIG can have a positive effect on the outcome of TSS. In one recent study, Kaul et al. (1999) compared 21 patients with streptococcal TSS treated in this way with 32 patients with the same disease as controls. The outcome measure was 30-day survival and the result was a significantly higher survival rate in the IVIG-treated group (67 vs 34%). In another study, it was shown that pooled immunoglobulin preparations obtained from different companies had titres against staphylococcal enterotoxins and TSST-1 and that specific anti-SEB antibodies from these preparations protected mice from a high lethal dose of SEB (LeClaire & Bavari, 2001). However, variations in anti-PTSAg antibody titres among different lots of IVIG have been reported (Norrby-Teglund et al., 1998). In order to obtain favourable results from immunomodulatory treatment of TSS or septic shock, it will therefore be necessary to determine the titres of specific antibodies against the relevant toxins in the IVIG as well as the initial antibody levels in patients.

References


