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 subclavicular 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). Interleukin 6 was 4·5 (normal 5–36). Arterial blood gases: pH 7·403, pCO2 36·4, pO2 52·8 and standard bicarbonate 22·1. A chest radiograph showed bilateral alveolar/interstitial infiltrates. Blood cultures and cutaneous lesions were positive for Staphylococcus aureus, fully sensitive to all antibiotics including penicillin.

A transthoracic echocardiogram was normal, but a transoesophageal examination showed large vegetations on the mitral valve leaflet, with moderate regurgitation (Fig. 1). She received treatment with flucloxacillin 2 mg i.v. every 6 h with gentamicin 80 mg i.v. every 8 h. However, she deteriorated rapidly and, by the third admission day was hypoten-sive and in respiratory failure, requiring inotropic support and assisted ventilation. On the fourth day, the serum creatinine had risen to 378 mmol l−1 (normal 53–88) and the white cell count to 38×109 l−1. D-dimers were >8000. The respiratory failure worsened, with an FiO2 requirement of 100% and peak end-expiratory pressure (PEEP) of 13 cm 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 5·6 l min−1 m−2 over the next 48 h. The systemic vascular resistance fell from 1112 to 816 dynes s cm−5 (normal 1970–2390) 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 was 7·38 (normal 7·35–7·45) and alkaline phosphatase 253 U l−1 (normal 50–136). Arterial blood gases: pH 7·403, pCO2 36·4, pO2 52·8 and standard bicarbonate 22·1.

References

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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 α-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 α-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-
compared with an expected mean of 5–7 days (Gentry, 1998), and this was reflected in the rapid sterilization of blood cultures by 48 h, for Antimicrobial Chemotherapy, 1998), and this was
with current guidelines (Working Party of the British Society
Our patient had optimal antibacterial treatment consistent
activity and control of clinically relevant bacterial mutations.
Surgery has a crucial role to play in the management of
staphylococcal endocarditis. Long-term survival is signifi-
cantly improved in patients treated medically/surgically
compared with those treated medically alone (Cassada et
Un fortunately, 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 pro-
portion (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
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
disease characterized by fever, hypotension, diffuse erythe-
ematous 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 (PTSAsgs),
whose most distinguishing property is their superantigeni-
city, i.e. the capacity to induce a disorderly, polyclonal
expansion of certain T-cell subpopulations. This results in
production of pathological levels of proinflammatory cyto-
kines 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 values, pro-
gressive shock and multiorgan involvement and haemody-
namic parameters suggestive of uncontrolled sepsis, despite
rapid sterilization of blood cultures, suggests that staphylo-
coccal toxins were at least as important as valvular dysfunc-
tion 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 enter-
otoxins, 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 staphylo-
coccal 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, how-
ever, 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
PTSAsgs 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 that
specific anti-SEB antibodies from these preparations pro-
tected 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 (Norby-
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.
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