

# *Staphylococcus aureus* toxic shock syndrome toxin-1 endocarditis with muscular metastatic abscesses

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## SUMMARY

A 42-year-old woman, living in a nursing home for the mentally disabled, with congenital ventricular septal defect and multiple comorbidities, developed endocarditis with vegetations of the interventricular septum and the right coronary aortic leaflet. The main feature of this case was the metastatic embolism leading to multiple and muscular abscesses. Methicillin-sensitive *S. aureus*, spa type 253 and ST30, producing toxin shock syndrome toxin-1 was isolated from blood cultures. The patient was initially treated with beta-lactam antibiotics without showing clinical response and subsequently with daptomycin and linezolid that improved the patient's clinical symptoms. The effectiveness of treatment with daptomycin and linezolid was partly due to the ability of linezolid to reduce TSST-1 secretion. The portal of entry of the infection was not recognized. TSST-1 production by the strain might have favoured the formation of large cardiac vegetations and the subsequent metastatic dissemination to the muscles.

**KEY WORDS:** Endocarditis, Toxic shock syndrome, Abscesses, Antibiotics.

Received May 12, 2013

Accepted November 26, 2013

## INTRODUCTION

*Staphylococcus aureus* is a versatile human pathogen causing infections ranging from relatively mild involvement of skin and soft tissues to life-threatening sepsis, pneumonia, and toxic shock syndrome (TSS). Infections are common both in the community and in hospital settings. Community-acquired *S. aureus* bacteremia frequently develops in the absence of a primary focus of infection and may result in endocarditis and secondary metastatic foci of infection (Finkelstein *et al.*, 1984).

*S. aureus* causes illness by invasion of tissues and production of exotoxins and secreted virulence factors. Among the staphylococcal exotoxins, there is a family referred to as "superantigens" on the basis of their unusual non-antigen-specific activation of T cells (McCormick *et al.*, 2001).

Superantigens include staphylococcal enterotoxin serotypes A-R and toxic shock syndrome toxin-1 (TSST-1). TSST-1 is associated with TSS, a serious condition typically characterized by fever, rash, desquamation, hypotension, and multisystem involvement (Centers for Disease Control and Prevention, 2011).

TSS results from the ability of the toxin to act as a superantigen, stimulating an uncontrolled immune-cell expansion and cytokine expression that bypasses normal MHC-restricted antigen processing (Lappin and Ferguson, 2009).

TSS occurs in both sexes and in children; in fe-

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males it is usually associated with menses, in particular due to tampon use during menstruation (Shands *et al.*, 1980). The incidence of non menstrual TSS has increased in recent years and is estimated to have a case fatality rate of 5% (Hajjeh *et al.*, 1999).

We report a case of sepsis associated with TSST-1-producing *S. aureus* that did not cause TSS but manifested with endocarditis (IE), metastatic lung embolisms and muscular abscesses.

## CASE REPORT

A 42-year-old woman, living in a nursing home for the mentally disabled, was admitted to the Division of Infectious Diseases because of fever. One week before admission chills, shortness of breath and generalized weakness had developed. Piperacillin/tazobactam had been administered intravenously for 5 days without any improvement. The patient had a ventricular septal defect (VSD) with left to right shunt, spastic tetraparesis, severe kyphoscoliosis, and partially surgically corrected clubfeet. In 1987 and in 1999 she was admitted to hospital for partial seizures with secondary generalization. Lichen planus and hypothyroidism were diagnosed in 2006.

Physical examination showed a heart rate of 110 beats/min, a grade 2/6 pansystolic murmur in the mitral area, a respiratory rate of 30 breaths/min, and tympanic temperature of 39.0 °C; blood pressure was 110/70. At lung auscultation, basal wet crackles and fine crepitations were present bilaterally.

Osler nodules were absent. Laboratory tests showed a white blood cell count of 25000/ $\mu$ L with a predominance of neutrophils, C-reactive protein was 18.41 mg/dL (normal value 0-0.75 mg/dL) and D-dimer was 1600 ng/mL (normal value <200 ng/mL). Chest X-ray showed bilateral pleural effusions. Transthoracic echocardiogram was normal. Blood cultures were performed and treatment with oxacillin 3 gr. i.v. every 6 hours was started.

On day 3 after admission, six blood cultures yielded methicillin-susceptible *S. aureus*; because of persistence of fever, gentamicin 240 mg i.v. once a day was added. The patient deteriorated and her respiratory rate worsened,

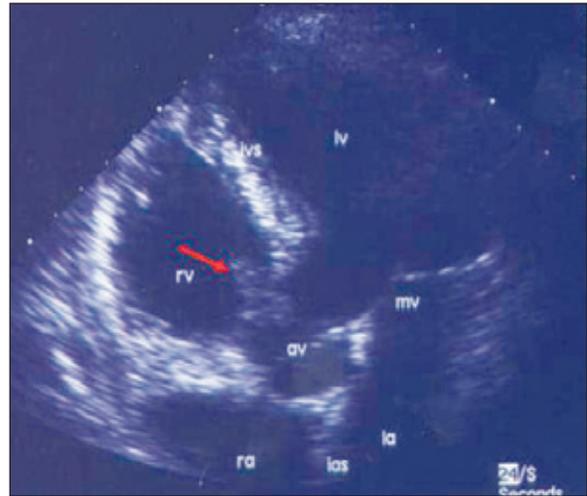


FIGURE 1 - Transesophageal echocardiogram. The arrow indicates a large vegetation adjacent to the ventricular septum defect.

with fever persisting between 37.8 and 39°C, although blood cultures were repeatedly negative. On day 10, a transesophageal echocardiogram (TEE) showed large vegetations adjacent to the septum defect and protruding into the right ventricle and a threadlike vegetation adherent to the septal leaflet of the tricuspid valve (Figure 1).

On the same day, a CT scan showed multiple parenchymal nodules of the lungs and abscesses in the left pectoralis major, subscapularis and iliocostalis muscles (Figure 2). Oxacillin and gentamicin were discontinued and therapy with linezolid 600 mg i.v. twice a day, daptomycin 8 mg/kg i.v. once a day, and meropenem 1 g i.v. three times a day was started. On day 17, TEE showed an increase in the interventricular septum vegetation with a mass size of 20x7 mm and a new vegetation in the right coronary aortic leaflet.

The patient was transferred to the Cardiothoracic Division of the University Hospital of Pavia for emergency surgery. However, on day 20, cardiac surgery was reconsidered since the haemodynamic conditions of the patient were stable, and she was transferred to the Division of Infectious Diseases at the same hospital. The antibiotic treatment was modified: linezolid and meropenem were discontinued and ceftazidime 2 g every 8 h was started. On day 21, chest and abdominal CT scan showed a reso-



FIGURE 2 - Axial contrast-enhanced computed tomography. The arrows indicate abscesses in (from the top): the pectoralis major, the subscapularis and the iliacus muscles.

lution of the lung nodules, but persistence of the abscesses in the muscles. Daptomycin was discontinued on day 23. On day 29, 200 ml of pus were drained from the abscess in the iliacus muscle. Culture of the pus was negative. On day 40, TEE showed complete resolution of the cardiac vegetations and an ultrasound examination showed resolution of the abscesses in the muscles.

A VSD repair was not considered due to the patient's multiple comorbidities. On day 50 ceftazolin was stopped; body temperature, white blood cell count, C-reactive protein, and coagulation tests were normal and the patient was discharged. She is still living in the nursing home for the mentally disabled in a stable cardiovascular condition.

## MICROBIOLOGICAL CHARACTERIZATION AND MOLECULAR TYPING

Blood cultures were processed in the microbiology laboratory of Lodi Hospital according to standard methods. Identification of the isolates and antimicrobial susceptibility tests were performed with an automatic system (Vitek 2; bioMérieux, Marcy l'Etoile, France). The *S. aureus* strain isolated from blood cultures was susceptible to most of the antibiotics tested including oxacillin (MIC 0.5 mg/L), rifampicin (MIC 0.5 mg/L), vancomycin (MIC 0.5 mg/L), linezolid (MIC 2 mg/L), and daptomycin (MIC 1 mg/L) according to the EUCAST breakpoints (The European Committee on Antimicrobial Susceptibility Testing, 2013), and was resistant only to penicillin, erythromycin and clindamycin. Using PCR assays the isolate was found negative for the Panton-Valentine leukocidin genes but positive for the *tst* gene, coding for TSST-1 (Monday and Bohach, 1999; Tinelli *et al.*, 2009). The MSSA strain was able to produce TSST-1 as demonstrated by a reversed-passive latex agglutination test (TST-RPLA, Oxoid-Thermo Fisher Scientific, Milan, Italy).

Molecular typing of the MSSA using multilocus sequence typing (MLST) and *spa* typing (Tinelli *et al.*, 2009), identified it as belonging to ST30, t253.

## DISCUSSION

Staphylococcal endocarditis is a serious illness with an overall mortality of 22–34% (Roder *et al.*, 1999). A major factor contributing to mortality is the frequent delay in diagnosis and treatment, due to the non-specific nature of the symptoms (Habib *et al.*, 2009).

VSD endocarditis is also uncommon and the diagnosis can be quite challenging (Di Filippo *et al.* 2004; Turhan *et al.*, 2005). IE is a common cause of pulmonary embolic abscesses but muscular abscesses are very unusual (Thadepalli and Francis, 1978; Gheysens *et al.*, 2012). The clinical presentation of this patient was intriguing. At hospital admission she presented with bilateral pleural effusions, but the IE diagnosis was not supported by the absence of Osler nodules and the negativity of TTE. The

isolation of MSSA from multiple blood cultures suggested IE but the diagnosis could only be confirmed by TEE on day 10.

Oxacillin was empirically administered to the patient; gentamicin was added when the blood culture result was available. A single daily dose regimen of gentamicin was preferred to the multiple doses regimen due to the better pharmacokinetics and lower nephrotoxicity of a single dose (Ferriols-Lisart and Alós-Alminaña, 1996).

Due to a deterioration in the patient's conditions, treatment was switched to linezolid, daptomycin, and meropenem. The addition of meropenem to two antibiotics specific for Gram-positive pathogens was aimed at broadening the spectrum of action to include Gram-negative organisms or anaerobes that can cause super-infections in a critically ill patient. A high dosage of daptomycin (8 mg/kg i.v. once a day) was administered to obtain a better outcome and a more rapid infection resolution than with a conventional dosage (Bassetti *et al.*, 2010). Cefazolin, a first-generation cephalosporin, was administered from day 24 to day 50, for its adequate activity against MSSA and its good penetration into infected tissues (Stevens *et al.*, 2005).

The MSSA strain causing IE in this patient was shown to produce TSST-1 and genotyping confirmed that the strain belonged to one of the most common staphylococcal clones (ST30) containing this toxin (Durand *et al.*, 2006). In this patient, the initial use of beta-lactam antibiotics apparently contributed to the lack of clinical response. Beta-lactam antibiotics may lead to an unfavorable outcome in TSST-1-associated staphylococcal infections by inducing toxin production. In infections associated with toxin-producing organisms, cell-wall-active agents such as beta-lactams, fail to suppress toxin production, in contrast to antibiotics that are protein-synthesis inhibitors. Beta-lactams can even increase concentrations of toxin, in particular TSST-1, since they cause lysis of the microorganisms and release of intracellular toxin (Stevens *et al.*, 2007).

Antibiotics that inhibit protein synthesis, such as clindamycin and linezolid, have been shown to decrease production of toxins, including production of TSST-1. These antibiotics may have

beneficial effects on outcomes by attenuating virulence-factor expression. Therefore treatment with linezolid can be more effective than treatment with a beta-lactam in case of toxin-producing *S. aureus* infections (Stevens *et al.*, 2006; Stevens *et al.*, 2007). As for daptomycin, there are no data regarding a possible impact on staphylococcal toxins. However, since this antibiotic targets bacterial membrane and cell wall (Bush, 2012) it is unlikely to affect toxin production.

The combination of daptomycin and linezolid has been advocated by some experts despite the lack of in vivo, in vitro and clinical data regarding their interaction (Hageman *et al.*, 2006). This combination has been considered at least of theoretical benefit in patients with methicillin-resistant staphylococcal bacteraemia and pneumonia that are failing vancomycin therapy (Nguyen and Graber, 2010). In this patient, the 10-day course of linezolid in association with daptomycin was apparently able to overcome the toxin-producing *S. aureus* strain inducing a favorable outcome.

Another noteworthy aspect of this case was the lack of typical TSS symptoms (hypotension, rash, exfoliation). It is known that not all patients colonised or infected with a TSST-1-producing strain of *S. aureus* develop TSS; this depends on the interaction between the pathogen and the host immune system (Lappin and Ferguson, 2009). However, the role of TSST-1 might have been important for IE development: TSST-1 producing strains have been shown to have higher ability to cause IE than TSST-1-negative isolates and to produce larger vegetations harbouring higher bacterial counts (Spaulding *et al.*, 2012). These features were likely favourable for metastatic embolization, and dissemination to the muscles. A possible tropism for the muscles of TSST-1-producing *S. aureus* should be further investigated.

The portal of entry of *S. aureus* in this patient was unknown, although being a resident of a long-term care facility she might have been predisposed to nasal colonization by *S. aureus*. In this patient TSST-1 serology was not evaluated. This is of limited importance since healthy adults may have antibodies to TSST-1 also in the absence of infection (Bonventre *et al.*, 1984). Our study has some limitations. First, we did

not perform microbiological tests to evaluate any additive or synergistic effects of the antibiotic combinations used for the patient's treatment (e.g. daptomycin plus meropenem). Second, we did not perform tests to evaluate the bactericidal activity of the antibiotics used against the *S. aureus* strain.

This unusual case of endocarditis emphasizes that both the clinical presentation and the characteristics of the microorganism are of great importance in the choice of a highly individualized antibiotic treatment.

#### ACKNOWLEDGEMENTS

The authors would like to thank the patient who consented to the publication of this report. A written informed consent was obtained for publication of the medical history and the accompanying images. We are grateful to Anna Maria Marella for editing the manuscript.

#### DECLARATION OF INTEREST

The authors declare that they have no competing interests. The authors alone are responsible for the content and the writing of this paper

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