Caso clinico

Case report

High dose of trimethoprim-sulfamethoxazole and daptomycin as a therapeutic option for MRSA endocarditis with large vegetation complicated by embolic stroke: a case report and literature review

Trimetoprim-sulfametossazolo e daptomicina a dosi elevate quale opzione terapeutica nel trattamento dell'endocardite da MRSA con vegetazioni estese complicata da stroke embolico: caso clinico e rassegna della letteratura

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INTRODUCTION

Staphylococcus aureus is one of the main causes of infective endocarditis (IE) in industrialised countries, and *S. aureus* endocarditis is often associated with several clinical manifestations and complications in the form of fever with metastatic infection, heart failure and central nervous system involvement [1-3]. An increasing proportion of *S. aureus* endocarditis cases are methicillin-resistant *S. aureus* (MRSA), and methicillin-resistance is on the rise in intravenous drug users who generally show less favourable outcomes after treatment, as well as more frequent and potentially life-threatening complications [3, 4].

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Large vegetation carries a poor prognosis and high mortality risk, especially if associated with MRSA infection [5]. Early diagnosis and immediate commencement of effective antibiotic therapy is imperative in saving lives. Although optimal medical management consists of antimicrobial medications, extensive and complicated cases of IE are currently mainly treated with parenteral antibiotics and cardiac surgery [6, 7]. To contribute to better management of severe complicated IE, in terms of determining treatment strategies, we describe a complex case of recurrent MRSA mitral valve endocarditis.

CASE PRESENTATION

In June 2010, a 35-year-old male HCV-positive intravenous drug user of Italian origin came to the Emergency Department of the Paolo Giaccone University Hospital, Palermo, with fever,

mental confusion and numbness of the limbs that he had been experiencing for five days. A review of his medical history revealed previous MSSA endocarditis and mitral valve repair surgery. A human immunodeficiency virus test performer on admission was negative.
Clinical examination revealed his blood pressure to be 100/80 mmHg and his pulse was 110 beats/min and regular. His electrocardiogram was unremarkable. Auscultation revealed a harsh 3/6 holosystolic murmur, best heard at the cardiac apex, radiating to the sternum. Initial laboratory tests showed a WBC count of 7.54×10^3/L (85.4% neutrophils, 9% lymphocytes, and 4.9% monocytes), Hb 12.8 g/L, ALT 53 U/L (normal range 5-45 U/L), AST 58 U/L (normal range 5-45 U/L), GGT 120 U/L (normal range 4-50 U/L), ALP 224 U/L (normal range 42-128 U/L) and serum C-reactive protein levels (CRP) of 15 mg/dl (normal range 0.08-1.5 mg/dl). Coagulation parameters, renal function and urine and OGTT were all normal.
The stroke team was alerted and the patient was given standard emergency room assessment and treatment. A CT image of the brain showed frontal and insular sub-arachnoid haemorrhage. His angiogram was normal. A transthoracic echocardiogram revealed a large vegetation 1 cm x 1 cm adhering to the mitral leaflets and protruding into the left atrium (Figure 1).
S. aureus DNA was detected by LightCycler SeptiFast and empiric intravenous antimicrobial treatment with vancomycin (35 mg/kg per day by continuous infusion) and gentamicin (5 mg/kg/day) was started [8].
12 hours after admission, the patient showed cardiac conduction abnormalities progressing to Mobitz type I second-degree atrioventricular block (ECG findings) and he was moved to the Cardiac Intensive Care Unit (CICU). The patient's condition steadily worsened and petechial exanthema appeared.
Blood culture grew MRSA. The antimicrobial susceptibility test was carried out using previously described methods, in accordance with Clinical and Laboratory Standards Institute guidelines [9]. The isolate was susceptible to cotrimoxazole (TMP/SMX), linezolid, tigecycline and daptomycin and resistant to rifampin, tetracycline, ciprofloxacin, piperacillin-tazobactam, aminoglycosides and macrolides. Vancomycin minimum inhibitory concentration (MIC) was 2 µg/ml. SCC*mec* type was determined using previously described primers and

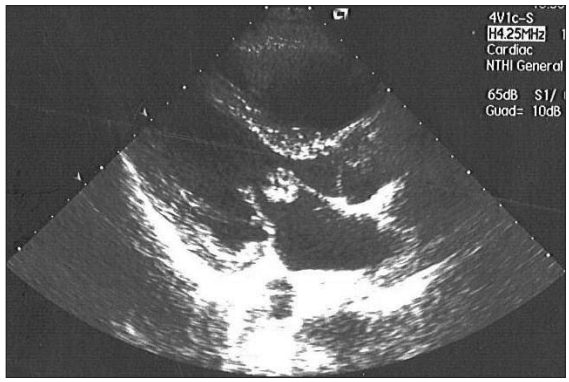

Figure 1 - Image along the parasternal axis. The large vegetation, about 1x1 cm, can be seen in the anterior leaflet of the mitral valve, causing outflow obstruction.

conditions (10). The isolate was attributed with SCC*mec* IVa.
We decided to shift antibiotic treatment to 8 mg/kg/day of daptomycin every 24 hours and 15 mg/kg/day of TMP/SMX administered intravenously in three equal doses. By the 25th day, the vegetation had reduced from 1 cm to 0.6 cm and the patient's clinical conditions had improved.
Considering the size of the vegetation, its hyper mobility and the associated systemic embolic event, surgical re-repair was judged to be essential and proposed to the patient. Nevertheless, despite our concerns for his health, he did not consent to cardiac surgery.
After six weeks of combination intravenous antibiotic treatment with daptomycin plus TMP/SMX, the patient was discharged on a high dose of TMP/SMX (320 mg/1,600 mg twice daily) for six weeks and referred for outpatient follow-up. High-dose TMP/SMX treatment was well tolerated in our patient throughout the treatment course. At the end of the prescribed course of treatment, the patient came back for a check-up: trans-oesophageal echocardiography showed that the vegetation had disappeared and edges had thickened.

DISCUSSION

Our results further contribute to showing that it may be difficult to follow guidelines on starting antimicrobial therapy because different MRSA isolates have varying antimicrobial susceptibility patterns in different geographic areas [10-12].

Because severe infections such as cerebral embolism in the course of infective endocarditis require quick and effective treatment, we resorted to SeptiFast to identify the isolate rapidly and adopt more accurate empiric treatment. In our patient's case, we believe the Septifast procedure was in support of microbiological diagnosis. Accurate identification of blood isolate and its antimicrobial susceptibility was central to the optimal management of our case report.

Our initial therapeutic approach was to suppose that the *S. aureus* strain was methicillin-resistant as the patient had a history of surgery, previous anti-staphylococcal treatment and chronic liver disease. Moreover, we took into account our recent epidemiology and the circulation patterns of MRSA clones, as well as the literature which frequently shows different antimicrobial susceptibility patterns of these strains [12]. Our patient's history and the phenotypic and molecular characteristics of the MRSA isolate would suggest a community strain, though susceptibility to non- -lactams and SCC*mec*IV have proved to be also shared by some epidemic clones of HA-MRSA, such as EMRSA-15, that are widely circulating in our geographic area [11].

For several years, glycopeptides have been considered the antimicrobials of choice for serious MRSA and methicillin-resistant coagulase-negative staphylococci (MR-CoNS) infections [13-15]. However, a literature search found no published studies of the effects of vancomycin exposure on outcomes and hospital costs in patients with complicated bacteraemia or IE due to MRSA.

In our patient's case, we initially considered continuous vancomycin infusion because this drug remains the first line antimicrobial for community-acquired and nosocomial infections due to MRSA, and because data support theoretical arguments that higher and more sustained serum levels of vancomycin, obtained by continuous infusion, may enhance clinical efficacy.

In our patient's case, the *S. aureus* isolate showed a vancomycin MIC of 2 mg/mL which was considered to be perhaps less effective against serious methicillin resistance, or a "bridge too far" in that the doses required carried a significant risk of toxicity [14]. Guidelines therefore recommend therapy with alternative antimicrobials [16].

Close *et al.* have recently shown that TMP-SMX 15 mg/kg/day is an option in the management of GISA infection [17]. Although some anecdotal reports suggest successful therapy with TMP-SMX for a variety of *S. aureus* infections, clonal outbreaks of MRSA resistant to TMP-SMX have been described [17-19]. The role of folate antagonist for treatment of MRSA infection has been recently suggested because TMP-SMX is bactericidal and well tolerated; it is antimicrobial with high tissue penetration that reduced cytokine production after SA toxin exposure [20]. It is also inexpensive. [19].

On the other hand, antimicrobial association against S. *aureus* may be chosen to increase bactericidal activity in cases of severe infection, especially during complicated IE. Over the decades, *in vitro* and *in vivo* studies of bactericidal interactions of antimicrobial molecules against *S. aureus* have yielded conflicting results [21].

Daptomycin is a well-known alternative treatment option for infective endocarditis; studies on the synergistic effects of daptomycin in combination with other antibiotics including gentamicin, rifampin, beta-lactams, TMP-SMX or clarithromycin present a new therapeutic approach [22-24]. In our case report, the antimicrobial susceptibility of the strain led us to combine new molecules like daptomycin with older, low cost antibiotics such as TMP/SMX. Moreover, the combination of TMP/SMX and daptomycin is justified by how they act synergistically to provide rapid bactericidal activity and reduce daptomycin resistance.

In conclusion, our case report could expand the clinician's understanding of contemporary drug therapy and represent a challenging case in currently-debated filed of research. Future studies are needed to evaluate available clinical and pharmacokinetic/pharmacodynamic (PK/PD) evidence regarding TMP/SMX, particularly in association with other antibacterials such as daptomycin.

Keywords: *Staphylococcus aureus*, infective endocarditis, antimicrobial combination.

SUMMARY

Large cardiac vegetation carries a poor prognosis and high mortality risk, especially if associated with methicillin-resistant *Staphylococcus aureus* (MRSA) infection. We share our experience of a rare and complicated large cardiac vegetation which had a favourable outcome with combination antibiotic treatment alone. A 35-year-old HIV-negative, HCV-positive male patient with a previous history of methicillin-susceptible *S. aureus* endocarditis showed MRSA mitral valve endocarditis with large vegetation, complicated by embolic stroke. The strain was soon identified by PCR but only after culture did the patient receive efficacious antibiotics. A combination of daptomycin plus trimethoprim/sulfamethoxazole (TMP/SMX) was administered for six weeks, followed by a high dosage of TMP/SMX for a further six weeks. Effectiveness of the treatment was demonstrated by the patient's clinical improvement and instrumental evidence of cardiac mitral vegetation clearance. Innovative antibiotic strategies in patient management are needed to fight *Staphylococcus aureus* endocarditis because strains show varying antimicrobial susceptibility patterns in different geographic areas. Timely initiation of targeted antimicrobial therapy remains a crucial step to reduce morbidity and mortality but culture is crucial for appropriate fine-tuning of antibiotic therapy.

RIASSUNTO

La presenza di un'estesa vegetazione cardiaca comporta una prognosi sfavorevole e un alto rischio di mortalità, soprattutto se questa è associata a un'infezione da Staphylococcus aureus *meticillino resistente (MRSA). Qui di seguito gli autori riportano un caso di endocardite su valvola mitralica da MRSA caratterizzata da un'estesa e mobile vegetazione (>1,2cm) e complicata da stroke embolico, in un paziente di 35 anni HIV-negativo, HCV-positivo con pregressa storia clinica di endocardite da S. aureus meticillino-sensibile (MSSA) ed intervento di* valve repair. *Lo* S. aureus *è stato inizialmente identificato con metodica di LightCycler SeptiFast, ma solo dopo esame colturale il paziente ha ricevuto una terapia antibiotica efficace. La combinazione di daptomicina e trimetoprim-sulfametossazolo (TMP/SMX) per via e.v. è stata somministrata per sei settimane e poi continuata nelle successive sei settimane con solo TMP/SMX ad alte dosi per os. L'efficacia del trattamento è stata dimostrata dal miglioramento delle condizioni cliniche del paziente e dalla* clearance *della vegetazione. Trattamenti antibiotici innovativi nella gestione del paziente sono necessari per contrastare le endocarditi da* S. aureus*, e in particolare da MRSA, poiché i ceppi hanno mostrato variegati profili di sensibilità agli antimicrobici in differenti aree geografiche del nostro paese.*

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