Disseminated methicillin-susceptible Staphylococcus aureus infection

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Abstract

Introduction. When clinicians think about Staphylococcus aureus bacteria, what comes to the mind of most is the dreaded methicillin-resistant form. However, clinicians should not forget the methicillin-susceptible type, which is just as virulent.

Case presentation. The authors present the case of a 20-year-old woman who was admitted with septic shock and multi-organ failure and was found to have disseminated methicillin-susceptible Staphylococcus aureus (MSSA) infection. The patient had persistent blood cultures positive for MSSA. A transesophageal echocardiogram showed a 1.1 cm vegetation in the mitral valve, and the patient had bilateral pleural effusions that grew MSSA. An MRI of the brain showed multiple areas consistent with infarctions thought to be secondary to septic emboli. The patient underwent a mitral valve replacement and was treated with a prolonged course of parenteral nafcillin.

Discussion. This case illustrates a severe clinical presentation and management of MSSA infections.

INTRODUCTION

Methicillin-susceptible Staphylococcus aureus (MSSA) bacteremia is extremely common among the human populace with around 20–30% of people being carriers. The carrier site is often the anterior nasal cavity with other sites including the skin, the pharynx and the gastrointestinal tract [1]. With the bacterium being such common flora in humans, treatment plans should not be unfamiliar to clinicians when this prevalent bacterium turns pathogenic. The clinical spectrum ranges from soft tissue infections to more severe and deep-seated infections as bacteremia, toxic shock syndrome, endocarditis, osteomyelitis, etc. MSSA bacteremia is associated with a high mortality rate of 23.3% [2]. Data from more than 70 million hospitalizations in the United States suggest that rates of S. aureus infective endocarditis (IE) have increased significantly [3].

CASE PRESENTATION

The authors present the case of a 20-year-old woman who presented for generalized pain, fever and altered mental status that was found to be in septic shock. She was seen in an urgent care clinic the day prior to presentation and diagnosed with streptococcus pharyngitis for which she was prescribed amoxicillin 500 mg PO bid. She had a past medical history significant for mitral valve prolapse diagnosed in childhood but was otherwise healthy.

On examination, the patient looked acutely ill and her vital signs were as follows: temperature 98.4 °F, heart rate 134 beats min⁻¹, respiratory rate 30 breaths min⁻¹ and blood pressure 94/46 mmHg. She was noted to be alert but oriented to self only. Her cardiovascular exam was unremarkable with normal S1 and S2 and no obvious murmur was heard. Her head and lungs did not exhibit abnormalities but her abdomen was diffusely tender with no palpable hepatosplenomegaly. She had multiple Janeway lesions on the palms and soles. Initial laboratory work-up was significant for white blood cell count 4.5×10⁹ l⁻¹, haemoglobin 13.1 g dl⁻¹, haematocrit 36.1%, platelet count 18×10⁹ l⁻¹, blood urea nitrogen 31 mg dl⁻¹, creatinine 1.38 mg dl⁻¹, bicarbonate 15 mEq l⁻¹, total bilirubin 2.6 mg dl⁻¹, alkaline phosphatase 45 IU l⁻¹, aspartate aminotransferase 170 IU l⁻¹, alanine aminotransferase 67 IU l⁻¹, albumin 2.4 g dl⁻¹, lactate acid 3.2 mmol l⁻¹, procalcitonin 32.22 and creatine kinase 4468 IU l⁻¹. The patient was HIV negative, and her blood cultures were positive for MSSA. A lumbar puncture was consistent with bacterial meningitis although cerebrospinal fluid cultures were negative. She also had bilateral...
pleural effusions that grew MSSA and had associated apical pneumothoraces that required temporary chest tube placement. Transesophageal echocardiogram exposed a 1.1 cm vegetation associated with the mitral valve near the medial commissure. An MRI of the brain highlighted multiple areas consistent with infarctions, which were thought to be secondary to septic emboli from the infective mitral valve endocarditis. The patient developed persistent MSSA bacteremia for a week and eventually underwent a mitral valve replacement with a bio-prosthetic valve with intraoperative cultures being positive for MSSA. The mitral valve measured 3.6×3.5 cm on pathologic gross exam and had thin white-tan leaflets with an attached 1.3×1.3×0.7 cm pink-tan nodule that was microscopically composed of extensive neutrophilic inflammation with necrotic debris and numerous aggregates of coccic bacteria, consistent with a vegetation of acute endocarditis (see Fig. 1 and Fig. 2 below). She was initially treated with broad spectrum antibiotic coverage and then de-escalated to nafcillin 12 gm IV in 24 h infusion. Then, 4 weeks after valve replacement, she developed a rash that was suspicious for delayed allergic reaction and she was transitioned to ceftriaxone 2 gm IV q12 hours to complete 8 weeks of parental antibiotic therapy from the time of mitral valve replacement. This was followed by suppressive therapy with doxycycline. Rifampin could not be used due to interaction with amiodarone. The patient had sensorineural hearing loss thought to be a sequela of meningitis and ultimately had bilateral cochlear device implantation.

**DISCUSSION**

This clinical vignette describes the case of a young woman who unfortunately suffered from disseminated MSSA infection which caused a myriad of sequelae including severe sepsis, endocarditis, meningitis with brain infarcts and empyema.

*S. aureus* is an extremely common pathogen causing bloodstream infection (BSI), and is the most common cause of IE in the developed world [3]. Nearly one half of patients documented to have *S. aureus* BSIs present with no known avenue of entry. A clinician should be aware of the high risk of septic metastases that BSIs can potentially cause [4]. The United States has an incidence of *S. aureus* bacteremia of approximately 1/2000 population, the highest of any country that was surveyed [5]. A meta-analysis comparing 11 different studies found that the majority of bacteremia cases were nosocomial, and the largest source of these infections were from intravascular devices and endocarditis [2]. IE caused by *S. aureus* has a higher rate of severe sepsis, debilitating neurological events, multiple organ failure and overall higher clinical morbidity compared to other microorganisms causing endovascular infection [6]. The risk of developing IE increases with the duration of time that the source of infection remains untreated due to an increased number of bacteria entering the bloodstream [3].

Existing studies show that individuals are more likely to acquire MSSA BSIs in a community setting, while the higher probability of nosocomial BSI etiology is methicillin-resistant *S. aureus*. The history of the patient in the setting of possible sepsis is vitally important when deciding treatments plans [7].

A significant take away point of this report is to express the vital importance of the immediate administration of appropriate antibiotics after culture identification with a change from the initial broad spectrum coverage for suspected sepsis. A study by Khatib *et al.* looked at the impact of initial antibiotic use on 342 patients with *S. aureus* bacteremia and vancomycin use on MSSA bacteremia caused a higher percentage of delayed clearance and higher in-hospital mortality [8]. This is not advocating stopping initial broad

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**Fig. 1.** Large mitral valve acute endocarditis vegetation, H&E x4.

**Fig. 2.** Vegetation with numerous aggregates of cocci bacteria, H&E x10.
spectrum antibiotics such as vancomycin when dealing with possible sepsis; rather, it suggests de-escalating as soon as blood culture susceptibilities are available.

It has been shown that the drug of choice for MSSA bacteremia is the semi-synthetic penicillinase-stable beta-lactam antibiotics such as nafcillin and cloxacillin [3, 4]. If the patient is allergic to penicillin, then alternatives can be vancomycin and the first generation cephalosporin: cefazolin. But as noted above, vancomycin is less effective in treating MSSA. With an allergy, cefazolin should be considered as it is comparable in efficacy to nafcillin, and superior in efficacy to vancomycin. It has been shown that some clinicians often continue empiric vancomycin treatment even after MSSA strains have been identified. This is a poor choice due to vancomycin’s very potent side effects such as nephrotoxicity, treatment failure, relapse, persistent bacteremia and probable infectious seeding [9]. In less serious MSSA infections involving soft tissue and skin: clindamycin, lincomycin and erythromycin have important roles.

As previously stated, cefazolin has very similar clinical efficacy compared to nafcillin in treating MSSA bacteremia, and is generally better tolerated with the only drawback being that it poorly penetrates the blood brain barrier. Clinicians should have heightened awareness of this because of the severe complications that could arise from MSSA bacteremia with disseminated metastatic foci, such as IE and meningitis. Cefazolin should not be used in these situations [10]. In this case, the patient received parenteral nafcillin most of the treatment, but she developed a severe rash suspected to be a delayed allergic reaction and was then transitioned to ceftriaxone rather than cefazolin given her initial presentation with meningitis and multiple brain septic emboli.

When treating a patient with disseminated MSSA BSI, the authors recommend an organ-based treatment approach [11]. Ruling out meningeal involvement, pneumonia, endocarditis, catheter or device-related infections, and osteomyelitis is of vital importance. Daptomycin at a dose of 6 mg kg⁻¹ once daily has been shown to be equivalent in efficacy to the standard therapy when treating endocarditis caused by S. aureus [12]. Although rifampin efficacy remains controversial, and the medical community is divided on its adjunctive use to treat MSSA infections; rifampin does have great success in accumulating and penetrating into Gram-positive bacteria and is also efficacious at breaking through biofilms. One study states that there is minimal data to support rifampin combination therapy for the treatment of non-mycobacterial infections [13]. However, a newer 2015 retrospective study from Finland, which included 357 S. aureus patients, found that adjunctive rifampin therapy improved the clinical outcomes of patients with deep-seeded S. aureus infections with therapy lasting 14 days and initiated within 7 days of a positive blood culture [14]. Thus, one should consider adjunctive therapy with rifampin in these situations. In the current case, rifampin was not given due to concomitant use of amiodarone (rifampin decreases serum concentrations of amiodarone).

Unfortunately, MSSA BSIs and bacteremias are not as clear cut as this and the optimal treatments are more complex and understandably based upon the complications of the infection and co-morbidities of the patient [11]. Therefore, the treatment of an individual patient needs to be based on their clinical presentation and course.

S. aureus bacteremia in general is associated with high percentages of IE. Community IE is caused mostly by MSSA, while nosocomial IE is largely caused by methicillin-resistant S. aureus. However, overall, MSSA causes higher rates of IE. Every patient found to be suffering from S. aureus bacteremia should be aggressively evaluated for IE [15] with transesophageal echocardiography superior to transthoracic echocardiography in making the diagnosis [11]. If there is a high suspicion of IE despite an initial negative transesophageal echocardiography, then a repeated test is recommended in 3 to 5 days or sooner if clinical findings change [3].

Screening for endocarditis should be highly pursued in persons with community acquisition of infection, native valvulopathy, prosthetic valve, intravenous drug use, history of prior endocarditis and unknown portal of entry. At least three sets of blood cultures from separate venipuncture sites should be obtained, with the first and last samples drawn at least 1h apart [3]. Blood cultures should be repeated following the start of anti-staphylococcal antibiotic therapy in order to document clearance and because they could prove a useful marker in providing more aggressive management and surgical resection of a valve in endocarditis cases [16].

Concerning surgical intervention, multiple factors should be considered including the size of the vegetation, presence of perivalvular infection, presence of embolism or heart failure, age, non-cardiac comorbidities and available surgical expertise. There is not yet clear evidence to define the optimal timing of valve surgery [3]. The decision for early cardiac surgery in this patient was determined by the multidisciplinary team based on her young age, no other comorbidities, large mitral valve vegetation, ongoing septic emboli and persistent bacteremia after 7 days of appropriate antibiotic therapy.

Patient follow-ups should be very scrupulous but within reason, and all organ systems should be evaluated (objectively and subjectively). It is extremely important to try to understand where the portal of entry of the bacteremia is taking place in order to properly treat the patient’s BSI. It is also important to distinguish the source as an unknown source can act as an undetected continuum of seeding giving rise to future complications [4].

Lastly, infection is three times more likely in patients who are carriers of S. aureus [17]. One study demonstrated that the majority of isolates from blood cultures in patients with S. aureus BSIs were indistinguishable from isolates from...
their anterior nares. So elimination of nasal carriage could potentially help prevent systemic BSIs [18].

In summary, this clinical vignette describes a case of disseminated MSSA with mitral valve endocarditis with multiple septic emboli to the brain and lungs. The patient had a mitral valve replacement with a bio-prosthetic valve and was treated with 8 weeks of antibiotic coverage for MSSA with resolution of her ailment.

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