A case report and literature review: osteomyelitis caused by community-associated methicillin resistant *Staphylococcus aureus*

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Abstract

Osteomyelitis in adolescents is a serious disease with the potential for lifelong disability. The key to successful management is early diagnosis, including bone sampling for microbiological and pathological examination to allow targeted and long-lasting antibiotic therapy. *Staphylococcus aureus* is the most frequently isolated microorganism in these patients. Methicillin-resistant *S. aureus* (MRSA) is usually considered a nosocomial pathogen, but increasingly it is acquired in the community. We present a case of acute osteomyelitis caused by community-associated MRSA (CA-MRSA) who had never been hospitalized and had no other known risk factors for MRSA. The changing epidemiology of MRSA became evident when infections occurred in previously healthy patients without established risk factors. MRSA infections have been increasingly reported in pediatric patients, but they are uncommon in adults. Skin and soft tissue infections remain the most common manifestations of CA-MRSA infections. Glycopeptides can be used as initial therapy and oral trimetoprim-sulfamethoxazole as sequential therapy for these patients.

Key words: *Staphylococcus aureus*; osteomyelitis; community-associated; methicillin resistant

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Introduction

Osteomyelitis is an inflammatory process accompanied by bone destruction and caused by an infecting organism. In any type of osteomyelitis, multiple bacterial organisms are usually isolated from the bone. The bacteriology is diverse, but *Staphylococcus aureus* remains the most commonly isolated organism [1].

*S. aureus* is a major cause of infections in both hospital and the community, causing diseases ranging from mild skin infections to fulminant septicemia and has become increasingly resistant to methicillin [2]. Methicillin-resistant *S. aureus* (MRSA) was first reported in the early 1960s and rapidly increased and spread in the 1980s. Today, MRSA is endemic in most hospitals in the world and accounts for 40-60% of all nosocomial *S. aureus* infections [3].

Community-associated MRSA (CA-MRSA) infections in both outpatients and inpatients are increasing in prevalence among adults and children. The Centers for Disease Control and Prevention (CDC) Active Bacterial Core Surveillance Program defined a CA-MRSA case as a patient with an MRSA infection who had no established risk factors. Established risk factors include the isolation of MRSA two or more days after hospitalization, a history of hospitalization, surgery, dialysis or residence in a long-term care facility within one year before the MRSA culture date, the presence of a permanent indwelling catheter or percutaneous medical device (e.g., tracheotomy or gastrostomy tube, or Foley catheter) at the time of culture; or previous isolation of MRSA [4].

Skin and soft tissue infections, such as abscesses or cellulites, remain the most common manifestations of CA-MRSA infections. Less commonly, CA-MRSA can cause severe diseases, such as necrotizing pneumonia, osteomyelitis, and septicemia. Most CA-MRSA infections resolve, but deaths from invasive CA-MRSA disease have been reported [5].

In this study, we present a case of acute osteomyelitis in an adolescent caused by CA-MRSA and discuss the emergence of MRSA as a cause of infection in the community in patients who have never been hospitalized and have no risk factors for MRSA infection. We also review the literature
Table 1. Number of osteomyelitis caused by CA-MRSA in other studies

| Study          | Number of osteomyelitis (%) |
|----------------|----------------------------|
| Hsu et al. [17] | 1 of 6 (16.7)              |
| Wu et al. [12]  | 2 of 17 (11.7)             |
| Jaggi et al. [18]| 5 of 49 (10.2)            |
| Ochoa et al. [19]| 7 of 159 (4.4)            |
| Fang et al. [20]| 1 of 29 (3.5)             |
| Lo et al. [21]  | 1 of 32 (3.3)              |
| Fridkin et al. [4]| 24 of 1,647 (1.5)        |

Concerning osteomyelitis caused by CA-MRSA and antibiotic susceptibility test results. To the best of our knowledge, this is the first case report from Turkey.

Case report

A previously healthy 17-year-old male adolescent was admitted to the University of Dicle Hospital, Diyarbakir, in the southeastern Anatolia region of Turkey with complaints of fever, inability to walk, erythema, local swelling, and pain on the left leg of ten days’ duration. His medical history was unremarkable.

On the day of admission, physical examination revealed that he was in pain and feverish (38.6°C). His physical examination was normal except for the musculoskeletal component. Lower extremities were neurovascularily intact. Local examination showed tenderness with increased local temperature, local swelling and erythema, and restricted movement of the left leg.

Laboratory findings included a hemoglobin level of 11.9 g/dl, total leukocyte count of 25,400/mm³ (87% polymorph nuclear cells), and a platelet count of 254,000/mm³. Erythrocyte sedimentation rate (ESR) was 140 mm/h with a C-reactive protein (CRP) measuring 60 mg/dl. In biochemical investigation, all tests were normal. Antinuclear antibody and Rheumatoid factor were negative. Serum C3, C4 and complement function were normal. Serum immunoglobulin concentrations were normal when measured during convalescence, showing that he did not have an obvious immunodeficiency. The Rose-Bengal and Widal tests were negative.

The patient’s history, physical examination, and imaging procedures suggested the possibility of osteomyelitis. A needle aspiration and bone biopsy were performed and the typical histopathological appearance of osteomyelitis was seen in the biopsy. Direct examination of the needle aspirate showed Gram-positive cocci. Bone, needle aspirate, blood, stool and throat cultures were obtained before the antibiotic treatment was started.

The patient was initially treated with cefazolin 3 g/day with no improvement. After three days, both the needle aspirate and bone cultures grew MRSA that was susceptible to erythromycin, gentamicin, ciprofloxacin, trimetoprim-sulfamethoxazole (TMP/SMX), vancomycin and teicoplanin. Its susceptibility was evaluated using disc diffusion testing at our clinic laboratory. Disk diffusion testing was performed as recommended by the National Committee for Clinical Laboratory Standards (NCCLS) [6]. Cefazolin was discontinued upon the return of needle aspirate and bone culture sensitivity results. Therapy was changed to intravenous teicoplanin 400 mg/day for two weeks, followed by oral TMP/SMX 480 mg twice daily for another four weeks. He responded well to treatment: his fever subsided three days after starting teicoplanin and the pain in his leg gradually improved. His ESR and CRP normalized within three weeks. He recovered completely at six months. X-ray examination showed sclerosis on the left leg. Follow-up after one year showed no residue from the osteomyelitis.

Discussion

The development of osteomyelitis is related to microbial and host factors. In osteomyelitis of any kind, the most important step is to isolate the offending organisms so that the appropriate antimicrobial therapy can be chosen [7]. Isolation can be achieved by direct biopsy from the involved bone. Material taken from an open sinus tract by swabbing will give misleading results because the isolates may include non-pathogenic microorganisms that are colonizing the site. However, it can be useful particularly when S. aureus is isolated [8]. In our patient, MRSA was isolated from both the needle aspirate and bone cultures. Osteomyelitis was also diagnosed by conventional radiography, bone scintigraphy, and bone biopsy.

The changing epidemiology of MRSA became evident when MRSA infections occurred in previously healthy patients without established risk factors for MRSA acquisition [3]. CA-MRSA disease incidence of 18 to 25.7 cases per 100,000 populations in the United States (US) has been reported [4].
| Antibiotics | Fridkin et al. [4] | Buck et al. [5] | Chen et al. [19] | Davis et al. [22] | Kim et al. [11] | Türeci et al. [18] | Ertug et al. [20] | Herold et al. [23] | Hsu et al. [17] | Uluğ et al. - CA-MRSA osteomyelitis [2] |
|-------------|-----------------|----------------|-----------------|-----------------|----------------|-----------------|-----------------|----------------|----------------|-------------------------------|
| Erythromycin | 18%             | 40%            | 8%              | 9%              | 17%            | 9%              | 3%              | 28%            | 50%            | 99%                           |
| Clindamycin | 87%             | 90.4%          | 95%             | 66.8%           | 17%            | 100%            | 3%              | 76%            | 50%            | 99%                           |
| Tetracycline | 88%             | 90.7%          | 100%            | 90%             | 38%            | 92%             | 93%             | 83%            | 83%            | 99.4%                        |
| TMP/SMX     | 97%             | 99%            | 100%            | 100%            | 96%            | 62%             | 100%            | 100%           | 100%           | 100%                         |
| Rifampin    | 98%             | 99.4%          | 100%            | 100%            | 89%            | 100%            | -               | -              | -              | 100%                         |
| Gentamicin  | 97%             | 98.4%          | 100%            | 96.7%           | 40%            | -               | 65%             | 56%            | 100%           | 100%                         |
| Ciprofloxacin | 65%           | 81.8%          | 84%             | 49.6%           | 46%            | 92%             | -               | -              | -              | 100%                         |
| Vancomycin  | 100%            | 100%           | 100%            | 100%            | 100%           | 100%            | 100%            | 100%           | 100%           | 100%                         |
| Linezolid   | 96%             | 100%           | 100%            | -               | -              | 100%            | -               | -              | -              | 100%                         |

Table 2. Antibiotic susceptibility of CA-MRSA isolates without risk factors in other studies.
It is now clear that the problem of CA-MRSA has become widespread as shown by reports from the US, Canada, Australia, Taiwan and Korea [3,4,9-11]. CA-MRSA infections have been increasingly reported (35-59%) in pediatric patients [3,12,13]. In contrast, they are uncommon in adults [3]. However, there are reports documenting that community-associated or outpatient MRSA infections may be increasing among adults [14-16], although it is unclear whether the isolates were obtained from patients with identified risk factors.

The predominant sources of the CA-MRSA isolates were skin, wound, abscess, and soft tissues. Osteomyelitis caused by CA-MRSA was seen rarely without identified risk factors (Table 1) [4,12,17-21].

In the present study, specimens of pus were cultured on sheep blood (5%), chocolate, and MacConkey agar plates. The plates were incubated at 37°C aerobically (MacConkey agar) and under 5% carbon dioxide (blood and chocolate agar) and examined at 24 and 48 hours. Identification of S. aureus isolates were based upon conventional techniques such as colony morphology, Gram stain, catalase and coagulase production, DNAse tests and Sceptor system (Becton-Dickinson, Maryland, USA). Methicillin resistance was tested by a modified Kirby-Bauer disk diffusion technique according to NCCLS guidelines [6]. Methicillin resistance was also confirmed by agar screen test using a Mueller-Hinton agar plate supplemented with 4% NaCl and oxacillin (6μgm/ml). In addition, the following antibiotics were tested: erythromycin, clindamycin, vancomycin, teicoplanin, tetracycline, gentamicin, ciprofloxacin, rifampin, and TMP/SMX. For our CA-MRSA isolates, antimicrobial susceptibility test results showed sensitivity to erythromycin, gentamicin, ciprofloxacin, TMP/SMX, vancomycin, and teicoplanin and resistance to the other antibiotics. Antimicrobial susceptibility test results from other studies are shown in Table 2 [4,5,11,17-20,22,23]. As can be seen in Table 2, antibiotic resistance rates were higher in the studies from Taiwan and Korea than from the US. This inconsistency may be explained by the overuse of these drugs.

In the present case, the patient was initially treated with cefazolin, but this was discontinued upon the return of needle aspirate and bone culture sensitivity results. It was changed to teicoplanin, followed by oral TMP/SMX. He responded well to the new treatment. For this reason, we suggest that oral TMP/SMX can be used as sequential therapy for these patients. Moazzez et al. [24] reported that the best empirical oral antibiotic therapy for patients with breast abscesses caused by CA-MRSA was TMP/SMX. Rutar et al. [25] also used TMP/SMX in CA-MRSA infections of the eye and orbit and patients had good visual outcomes. Additionally, Chen et al. [2], Lu et al. [26] and Marcinak et al. [27] stated that infections of CA-MRSA can be treated with TMP/SMX.

Death from CA-MRSA infections is very rare. In fact, there were no deaths in articles published before the 1999 report of four pediatric deaths resulting from CA-MRSA infection [28].

Conclusion

CA-MRSA infections are now common and a serious problem in most developing countries. Those infections usually involve the skin, especially among children, and hospitalization is common. Clinicians should be aware of possible serious CA-MRSA infections in persons without previously recognized risk factors. We suggest that the widespread use of antibiotics may have contributed to the remarkably high resistance rates of CA-MRSA. Consequently, more work is clearly required to define the epidemiology of this problem locally, and continued surveillance of the situation at national levels seems advisable. Furthermore, we need to develop appropriate prevention, referral, detection, and treatment guidelines for outpatients.

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