A Case of Community-Onset Meningitis Caused by Hospital Methicillin-Resistant Staphylococcus aureus Successfully Treated with Linezolid and Rifampicin

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Key Words
Methicillin-resistant Staphylococcus aureus · Meningitis · Linezolid · Rifampicin · Kuwait

Abstract
Objective: To report a relatively rare presentation of methicillin-resistant Staphylococcus aureus (MRSA) meningitis in a previously healthy boy in Kuwait. Clinical Presentation and Intervention: A 14-year-old boy presented with a 2 weeks’ history of headache and fever with increasing severity. He developed photophobia and double vision 2 days prior to his hospital visit and received ceftriaxone for 6 days prior to admission to the hospital. There was no history of head trauma or neurosurgical operation. Lumbar puncture revealed a slightly turbid cerebrospinal fluid with pleocytosis and greatly reduced glucose, elevated protein level and on culture grew MRSA. Staphylococcal chromosome cassette mec (SCCmec) typing revealed that it belonged to SCCmec type III and sequence type 238 (ST238-SCCmec-III). Polymerase chain reaction screening for the presence of Panton-Valentine leukocidin (PVL) genes yielded a negative result; all these findings were consistent with hospital-acquired MRSA.

He was treated with intravenous linezolid and rifampicin for 2 weeks, made good response and was discharged home fully recovered and well. Conclusion: Hospital MRSA should be considered in the differential diagnosis of the causative agents of community-onset meningitis in healthy patients even without predisposing factor.

Introduction

Staphylococcus aureus is an uncommon etiological agent of acute bacterial meningitis. Two different mechanisms of pathogenesis have been described in staphylococcal meningitis: postoperative meningitis which is associated with neurosurgical procedures, shunt insertion or head trauma and hematogenous meningitis secondary to parameningeal infection or staphylococcal infection outside the central nervous system (CNS). Infections caused by methicillin-resistant S. aureus (MRSA) are increasingly prevalent worldwide, particularly in hospital settings. However, MRSA only emerged as a cause of community-acquired MRSA infections in the
1990s. Until recently, most cases of staphylococcal meningitis were caused by methicillin-susceptible *S. aureus* isolates, but there have been a few reports of MRSA strains causing meningitis [1] arising from distant foci. Meningitis due to MRSA presents a therapeutic challenge in the choice of an appropriate antimicrobial agent for the initial treatment. Because of the rarity of staphylococcal meningitis cases in our country and indeed in many other countries around the world, it is conceivable that the role of *S. aureus* will remain obscure as there is no available data, including MRSA meningitis. In this report, we present a new case of partially treated meningitis caused by MRSA in a 14-year-old boy who did not have bacteremia or neurosurgery and who made a full recovery after treatment with linezolid and rifampicin.

**Case Report**

A 14-year-old Kuwaiti boy was admitted to Mubarak Al Kabir Hospital, Kuwait, on September 15, 2008 due to severe headache, fever, photophobia and double vision. This previously healthy boy’s headache and fever began 2 weeks before presentation to our hospital and had progressively increased in intensity. This was followed by photophobia and double vision 2 days prior to admission. He had no past medical history of head trauma, surgery or drug addiction. A travel to Syria with his parents was the only relevant travel history. He received many antibiotics from different hospitals, including ceftriaxone injection 500 mg twice daily for 6 days with little or no improvement before the onset of photophobia and double vision. Unfortunately, other previous antibiotics administered were unknown.

On examination, he was alert, oriented, with a temperature of 37.7°C. His blood pressure was 120/72 mm Hg, pulse rate 78 beats/min and respiratory rate 15 breaths/min. Examination of the cardiovascular, abdominal and respiratory systems was normal. There was no neck stiffness. Examination of the cranial nerves showed left sixth nerve palsy with bilateral papilledema, which was more apparent on the left side (fig. 1). The rest of his CNS examination was normal. His complete blood count showed slight leukocytosis, white blood cell count 12.7 × 10^9/l, hemo-
globin 14 g/dl and platelets 471 × 10^9/l. The renal, liver, and lipid function tests were within normal limits and his C-reactive protein was 2.381 mg/dl (normal range 0–0.80 mg/dl). A computed tomography scan of head, sinuses and facial bones revealed no evidence of bleeding, fracture, mass effect or infarct. Magnetic resonance imaging and magnetic resonance venography failed to reveal brain stem pathology, hydrocephalus or cerebral venous thrombosis. One set of blood was drawn for culture and another for hematology and biochemistry analysis. Lumbar puncture was performed and cerebrospinal fluid (CSF) was sent for microscopy, culture and susceptibility testing and biochemistry. The CSF was slightly turbid and microscopic examination revealed pleocytosis with a cell count of 120 leukocytes/mm³, predominantly polymorphonuclear cells, and red blood cells of 5/mm³. Gram stain and Ziehl-Neelsen stain of CSF did not reveal any microorganisms. CSF biochemical profiles revealed glucose level of 4.1 mmol/l, compared with serum glucose of 9.8 mmol/l and protein of 248 mg/l. Latex agglutination test to detect Streptococcus pneumoniae, Neisseria meningitidis and Haemophilus influenzae was negative. CSF was cultured on blood agar, chocolate agar as well as in, according to our routine practice, BACTEC blood culture bottle (bioMérieux, Marcy-l’Etoile, France). A provisional diagnosis of partially treated meningitis was made and the patient was started on intravenous (i.v.) ceftriaxone, 2 g every 12 h.

On day 2 of admission, his preliminary CSF culture in the BACTEC bottle revealed the growth of S. aureus. Subsequently, i.v. vancomycin 1 g every 12 h was then added to his antibiotic regimen. Next day (day 3), susceptibility results of the S. aureus isolate revealed a MRSA sensitive to vancomycin, teicoplanin, rifampicin and linezolid. However, the patient developed itching in the scalp and puffiness of the face, which was suspected to be due to vancomycin allergy. Consequently, his antibiotic regimen was modified to i.v. linezolid 600 mg every 12 h and rifampicin 600 mg once daily. Infection control policy for MRSA infection was initiated and the patient moved into an isolation room in the ward; standard MRSA body screening of the nose, axilla, groin, throat and the skin of the lumbar puncture site was carried out. The blood and urine cultures taken before commencement of antibiotics remained negative. He was investigated for a possible focus of his infection. There was neither external focus nor evidence of intra-abdominal collections. A transthoracic echocardiogram and chest X-ray were normal and the MRSA screen was negative. The patient improved steadily throughout the remainder of his admission; his fever, headache, photophobia as well as double vision disappeared after the third day of therapy. He received a total of 14 days of i.v. linezolid with rifampicin. The patient was sent home on no antibiotics after completing 2 weeks of therapy and he was well without any neurological complications. The patient was reviewed in the medical outpatient department 1 month after discharge. He was entirely healthy with complete resolution of his left sixth nerve palsy and papilledema (fig. 1).

**Microbiological Characterization of the MRSA Isolate**

The MRSA isolate was characterized for its susceptibility to antibacterial agents, staphylococcal chromosome cassette mec (SCCmec) type [2] and multi-locus sequence (ST) type [3]. It was also tested by polymerase chain reaction (PCR) for the carriage of genes for Panton-Valentine leukocidin (PVL) as described previously [4]. Methillin resistance was confirmed by detecting PBP2a in culture supernatant using a rapid latex agglutination kit (Denka-Seiken, Japan) according to the manufacturer’s instruction. It was positive for penicillin-binding protein 2a and was resistant to penicillin, oxacillin, gentamicin, kanamycin, amikacin, streptomycin, erythromycin, clindamycin, tetracycline, minocycline, ciprofloxacin and fusidic acid. It expressed low-level resistance to mupirocin but was susceptible to vancomycin, rifampicin, teicoplanin and linezolid. SCCmec typing revealed that it belonged to SCCmec type III and multilocus sequence typing showed it belonged to sequence type 238 (ST238-SCCmec-III). PCR screening for the presence of PVL genes yielded a negative result.

**Discussion**

*S. aureus* meningitis has been estimated to account for 3% of cases of bacterial meningitis in adults [1]. Different sources of infections have been associated with the hematogenous spread of *S. aureus* to the meninges in community-acquired cases, including surgical site infection, endocarditis, epidural/paraspinal abscess, skin/soft tissue infection, pneumonia, urinary tract infection, peritonitis, sinusitis, otitis media and osteomyelitis [1].

In the present report, we described a 14-year-old boy with culture-proven MRSA meningitis. While our search for a potential focus of infection in this patient remained negative, results of the microbiological investigations supported our provisional diagnosis that MRSA was the cause of this patient’s meningitis. The patient’s laboratory investigations, including the results of his CSF findings, such as the presence of pleocytosis (120 leukocytes/mm³) and a relative decrease in CSF/blood glucose (4.1/9.8) were all consistent with partially treated meningitis. The absence of detectable bacteria in the Gram stain of the CSF sample is not unusual since other groups have only been able to document positive CSF Gram stains in only 20% of cases of MRSA meningitis [5]. MRSA was isolated from the enrichment broth of the BACTEC blood culture bottle and not from the primary culture of the CSF. This may be related to the fact that the patient received multiple antimicrobial agents before admission to our hospital. While our clinical and laboratory data suggest that this patient had ‘spontaneous’ bacterial meningitis, we were unable to define the origin of his infection. The patient’s blood culture before antibiotic therapy was negative as well as his MRSA body screening of various colonization sites, and our extensive workup in hospital yielded no significant abnormalities explaining the source of his MRSA.
After obtaining the results of the culture and sensitivity of the CSF, we switched to a combination of linezolid and rifampicin to treat this patient, partly because the patient was allergic to vancomycin and most importantly because of its unpredictable achievable CSF level. One critical factor in treating a patient with meningitis is the penetration of certain antibiotics into the CSF. We elected to add rifampicin to linezolid given the known activity and susceptibility of this drug against MRSA and its ability to cross the blood-brain barrier. There had been an earlier report [6] regarding the use of linezolid for the treatment of CNS infections caused by Gram-positive cocci including MRSA meningitis, methicillin-resistant Staphylococcus epidermidis meningitis, vancomycin-resistant Enterococcus faecium meningitis and MRSA and methicillin-resistant S. epidermidis ventriculitis, in which the use of linezolid resulted in the resolution of the CNS infection.

Popovich et al. [7] had reported increased incidence of infections caused by MRSA as a community-acquired pathogen. Emergency department visits for purulent skin and soft tissue infections caused by community-acquired MRSA are on the increase, suggesting that this strain has added to the overall burden of serious S. aureus skin and soft tissue infections. MRSA has also emerged as a cause of severe community-acquired pneumonia, often associated with influenza and affecting children and young adults.

Prior to this report, only 2 cases [8, 9] of spontaneous MRSA bacterial meningitis without previous neurosurgical operations, nearby infection or bacteremia have been reported in the literature. The first case was a 24-year-old healthcare worker whose CSF yielded the growth of MRSA without any underlying cause. She was successfully treated with vancomycin and rifampicin [8]. The second case was an AIDS patient who had no past history of neurosurgical procedures or head trauma and was successfully treated with i.v. vancomycin [9].

One of the defining characteristics of community-acquired MRSA is the susceptibility to non-β-lactam antibiotics. However, a clone of community-acquired MRSA, termed USA300 strain, has been reported to be multiply resistant to the β-lactams, clindamycin, erythromycin, tetracycline, levofloxacin, and mupirocin [10]. The possibility that USA300 or its closely related clone USA400 might have surfaced in Kuwait made us investigate the genotype of our isolate. MRSA associated with community transmission most commonly carry SCCmec type IV, although this genetic element is not unique to these strains [11], our isolate carried SCCmec type 111 and lacked the genes for PVL toxin often associated with community-acquired MRSA. These characteristics, together with the multidrug-resistant nature of our isolate, are consistent with hospital-acquired MRSA, suggesting that our patient was infected by a hospital strain with community onset. Another interesting observation came from multilocus sequence typing, which showed that the isolate was ST238, indicating that it belonged to a rare MRSA clone. MRSA with this sequence type 238 has only been previously isolated from a patient in Bangkok, Thailand in 2003 [12]. South East Asian countries are popular vacation spots for a large number of indigenes and importation of such strains cannot be ruled out although the travel history of our patient and other members of his family did not reveal visits to any of the South East Asian countries recently.

**Conclusion**

We have reported a case of community-onset staphylococcal meningitis in a 14-year-old boy caused by an MRSA strain, whose characteristics are consistent with hospital-acquired MRSA, belonging to a rare sequence type (ST238). MRSA meningitis should be considered in the differential diagnosis of bacterial meningitis and linezolid combined with rifampicin may be the drug of choice for therapy, particularly in case of vancomycin allergy. A clinical trial of linezolid versus a comparator like vancomycin should be useful in addressing the role of linezolid in CNS infections.

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