Central nervous system invasion by community-acquired meticillin-resistant *Staphylococcus aureus*

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We report a case of community-acquired meticillin-resistant *Staphylococcus aureus* (CA-MRSA) bacteraemia with cavernous sinus thrombosis, meningitis and brain abscess in a previously healthy American, who was employed in Belgium. We consecutively reviewed all published cases of CA-MRSA with central nervous system (CNS) involvement. A total of 12 similar cases were found, of which 11 were published in the last 4 years. Predominantly, young previously healthy subjects were affected (median age 28 years). The cases involved brain abscesses (5/12), disseminated disease (4/12), cavernous sinus thrombosis (2/12) and other (1/12). Infection origins were superficial skin infections (5/12), mostly of the face, sinusitis (1/12), otitis media (1/12), other or unknown (5/12). Although, in our review of the literature patients treated with linezolid had a better outcome compared to patients treated with vancomycin, the latter is still the mainstay of therapy for CNS infections associated with MRSA.

**Introduction**

Although historically considered as a typical nosocomial pathogen, meticillin-resistant *Staphylococcus aureus* (MRSA) has rapidly emerged as a cause of infections in the community. In Europe, the prevalence of infections due to community-acquired (CA)-MRSA is lower than in the United States, although recent reports highlight that these infections are on the rise (Wallin et al., 2008). Most commonly, CA-MRSA causes skin and soft-tissue infections, while severe and life-threatening infections, such as necrotizing pneumonia, necrotizing fasciitis and severe sepsis, represent rare cases (Wang et al., 2005). We report a case of CA-MRSA bacteraemia with cavernous sinus thrombosis, meningitis and brain abscess in a previously healthy American. We consecutively reviewed all cases of CA-MRSA with central nervous system (CNS) involvement available in the literature.

**Case report**

A 34-year-old American man (from Texas), employed in Belgium, presented at the emergency department (GZA Hospitals, Antwerp, Belgium) with an excruciating headache, which he had been suffering from since the morning before his admission. His past medical history showed a cleft palate operation in childhood, and chronic sinusitis. He had not been recently hospitalized. The pain was localized at the left occipital region, radiating to the left eye, and accompanied by diminished vision with scotomas and vertigo. On clinical examination, no abnormalities were found. All routine laboratory tests were normal except for a C-reactive protein level of 28.9 mg l\(^{-1}\) (normal level 0 – 10 mg l\(^{-1}\)). A computed tomography (CT) scan of the brain without contrast was normal. Subsequently, he was treated with ibuprofen, which had no effect on the patient’s headache.

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The next day, the patient developed fever (39 °C). An examination carried out by an ear nose throat physician was negative for acute sinusitis. A chest X-ray of the patient was normal. Because of minor meningeal signs, a cerebrospinal fluid (CSF) analysis was performed and showed a white cell count of 2 \(\times 10^9\) cells l\(^{-1}\), a total protein level of <0.1 g l\(^{-1}\), a glucose concentration of 530 mg l\(^{-1}\) and a lactate level of 1.09 mmol l\(^{-1}\), with negative bacterial and fungal cultures. Amoxicillin–clavulanate was administered (2 g amoxicillin + 200 mg clavulanate every 8 h, intravenously).
On the third day after admission, increasing meningeal signs developed. A second CSF showed a white cell count of $618 \times 10^9$ cells $\text{l}^{-1}$ with $556 \times 10^9$ polymorphonuclear cells $\text{l}^{-1}$, a total protein level of $0.81 \text{ g l}^{-1}$, a glucose concentration of $780 \text{ mg l}^{-1}$ and a lactate level of $2.02 \text{ mmol l}^{-1}$. Gram stain analysis was negative, and cultures remained sterile. Meanwhile, blood cultures taken the day before grew MRSA. The strain was sensitive to gentamicin, amikacin, clindamycin, vancomycin, linezolid, co-trimoxazole, levofloxacin and rifampicin, and resistant to fusidic acid and erythromycin, using disc diffusion testing. Vancomycin was started at a dose of $1000 \text{ mg}$ every 12 h. Screening of the nose, axillae and groin were all positive for MRSA.

After 3 days of clinical improvement, the patient again developed fever, gradually lost decorum, was confused, and eventually developed stupor. New blood cultures were analysed and they grew MRSA. Gentamicin and rifampicin were added to the treatment regime. Daily doses of vancomycin were increased according to measured levels and administered by continuous intravenous infusion. Vancomycin levels varied between 12.3 and 24.2 mg $\text{l}^{-1}$, and daily dosages of vancomycin needed to be increased up to 4000 mg.

A transoesophageal echocardiography did not reveal vegetations or other abnormalities. A CT scan was taken and it showed defects in the brainstem, thalamus and frontal cortex. After contrast injection, a bilateral thrombosis of the cavernous sinuses was detected, and an extracranial collection in the parietal region, an obliteration of the maxillary sphenoidal sinus, and of several ethmoid cells became evident (Fig. 1). Four days later, a surgical drainage of the sinuses was performed. Unfortunately, culture of the pus was not performed. Eventually, the patient was transferred to the USA where he died despite further treatment with vancomycin, rifampicin and daptomycin.

MIC determination of vancomycin and linezolid was performed on the MRSA strain isolated from the first positive blood cultures by Etest (bioMérieux) with 0.5 McFarland inoculum on Mueller–Hinton agar after 24 h incubation. Vancomycin and linezolid MICs were 1.5 and 3 mg $\text{l}^{-1}$, respectively.

By molecular typing, the MRSA strain had PFGE pattern A23, identical to the reference CA-MRSA strain USA300 NSR384 (www.narsa.net), after Smal macrorestriction analysis (Denis et al., 2005). By spa typing, the isolate exhibited spa type t008 and carried staphylococcal cassette chromosome mec (SCCmec) type IV (Strommenger et al., 2008). PCR testing was positive for Panton–Valentine leukocidin genes (PVL) and for the arcA gene as a part of the arginine catabolic mobile element (ACME) cluster.

**Discussion**

Only recently, CA-MRSA was found to cause CNS infection. In the last 4 years, 11 reports of CA-MRSA CNS disease have been published (Table 1). Since our patient was employed in Belgium, but was frequently travelling between Europe and the USA, our strain likely originated from the USA, where the USA 300 (ST8) clone predominates. CA-MRSA clones circulating in Europe are more diverse and heterogeneous (Wallin et al., 2008). In 2002–2003, the majority of MRSA strains causing community infections in Belgium were of the ST80–SCCmec IV genotype (Denis et al., 2005). This new, and severe clinical entity, like others mentioned above, predominantly affects young previously healthy subjects (median age of published cases 28 years). As in the other published cases with CNS involvement, the known risk factors for infection with CA-MRSA were largely absent in our patient (Wallin et al., 2008).

The patient in our case probably suffered from CA-MRSA bacteraemia of unknown source with dissemination.
<table>
<thead>
<tr>
<th>Case reference</th>
<th>Country</th>
<th>Age</th>
<th>Sex</th>
<th>Year</th>
<th>Underlying disease</th>
<th>Mode of acquisition</th>
<th>Involvement</th>
<th>Type</th>
<th>CSF/abscess culture</th>
<th>Antibiotic used</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Khan et al. (2000)</td>
<td>UK</td>
<td>52 years</td>
<td>F</td>
<td>2000</td>
<td>Myocardial infarction, recurrent sinusitis</td>
<td>Sinusitis, facial cellulitis?</td>
<td>Cerebritis, brain abscess</td>
<td>EMRSA 16</td>
<td>Abscess +</td>
<td>Benzylpenicillin, chloramphenicol, metronidazole, flucloxacillin, vancomycin, trimethoprim, fusidic acid</td>
<td>Dysphasia secondary to cerebral damage</td>
</tr>
<tr>
<td>Pistella et al. (2004)</td>
<td>Italy</td>
<td>47 years</td>
<td>M</td>
<td>2004</td>
<td>None</td>
<td>Seeding from valve infection</td>
<td>Cerebritis, endocarditis, spleen infarction, minimal pleurisy</td>
<td>II : : B : : E</td>
<td>–</td>
<td>Vancomycin, amikacin, linezolid, ciprofloxacin, clarithromycin</td>
<td>Complete resolution</td>
</tr>
<tr>
<td>Wang et al. (2005)</td>
<td>Taiwan</td>
<td>6 years</td>
<td>F</td>
<td>2005</td>
<td>None</td>
<td>Osteomyelitis with haematogenous spread</td>
<td>SSI, bone, lung, brain infarction</td>
<td>–</td>
<td>CSF−</td>
<td>Vancomycin, trimethoprim–sulfamethoxazole</td>
<td>–</td>
</tr>
<tr>
<td>Rutar et al. (2005)</td>
<td>USA</td>
<td>44 years</td>
<td>M</td>
<td>2005</td>
<td>None</td>
<td>Pustule in naris</td>
<td>Cavernous sinus thrombosis, pansinusitis</td>
<td>USA300?</td>
<td>CSF−</td>
<td>Vancomycin, trimethoprim–sulfamethoxazole, rifampicin, metronidazole, ceftriaxone, Ampicillin, cefotaxime</td>
<td>Blindness in both eyes with deterioration</td>
</tr>
<tr>
<td>Martin et al. (2006)</td>
<td>India</td>
<td>16 years</td>
<td>F</td>
<td>2006</td>
<td>None</td>
<td>–</td>
<td>Brain abscess</td>
<td>–</td>
<td>Abscess +</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Ho et al. (2007)</td>
<td>China</td>
<td>Adult</td>
<td>–</td>
<td>2007</td>
<td>None</td>
<td>–</td>
<td>Meningitis, other?</td>
<td>–</td>
<td>–</td>
<td>Vancomycin, cefotaxime, rifampicin</td>
<td>Died 7 days after admission</td>
</tr>
<tr>
<td>Sifri et al. (2007)</td>
<td>USA</td>
<td>37 years</td>
<td>F</td>
<td>2007</td>
<td>None</td>
<td>Furunculosis neck and axilla, injection drug use</td>
<td>Brain abscess, brain infarctions</td>
<td>USA300, PVL+</td>
<td>Abscess +</td>
<td>Vancomycin, metronidazole</td>
<td>Died 4 days after admission</td>
</tr>
<tr>
<td>Enany et al. (2007)</td>
<td>Egypt</td>
<td>50 years</td>
<td>M</td>
<td>2007</td>
<td>Chronic hepatitis and diabetes</td>
<td>–</td>
<td>Brain abscess</td>
<td>ST30, PVL+</td>
<td>Abscess +</td>
<td>Vancomycin</td>
<td>Died</td>
</tr>
<tr>
<td>Munchkof et al. (2008)</td>
<td>Australia</td>
<td>26 years</td>
<td>M</td>
<td>2008</td>
<td>None</td>
<td>Concrete shrapnel injury to nostril</td>
<td>Meningitis with cavernous sinus thrombosis</td>
<td>ST93, PVL+</td>
<td>CSF+</td>
<td>Vancomycin, ceftriaxone, gentamicin, trimethoprim–sulfamethoxazole, rifampicin, linezolid</td>
<td>Complete resolution</td>
</tr>
<tr>
<td>Valentini et al. (2008)</td>
<td>Italy</td>
<td>15 years</td>
<td>M</td>
<td>2008</td>
<td>Mild asthma, Factor V Leiden deficiency</td>
<td>Skin infection on patient’s back?</td>
<td>Meningitis, thrombosis of vena cava inferior, vena iliaca, necrotizing pneumonia</td>
<td>USA300, PVL+</td>
<td>CSF+</td>
<td>Clarithromycin, ceftriaxone, ampicillin, doxycycline, acyclovir, vancomycin, teicoplanin, linezolid, rifampicin</td>
<td>Good general conditions</td>
</tr>
<tr>
<td>This case Belgium</td>
<td>Belgium</td>
<td>34 years</td>
<td>M</td>
<td>2008</td>
<td>None</td>
<td>Chronic sinusitis? Cryptogenic bacteraemia?</td>
<td>Cavernous sinus thrombosis + brain infarctions</td>
<td>USA300, PVL+</td>
<td>CSF−</td>
<td>Vancomycin, rifampicin, gentamicin, daptomycin</td>
<td>Died</td>
</tr>
</tbody>
</table>

F, Female; M, male.
towards the cavernous sinus and brain. Compared to PVL-negative S. aureus, PVL-producing S. aureus isolates, as was the case in our strain, may be associated with a greater likelihood of metastatic infection (Saginur & Suh, 2008). Since S. aureus bacteraemia is notorious for endocarditis and subsequent septic embolization, a transoesophageal echocardiography was performed, but was normal. A second hypothesis might be that chronic sinusitis, complicated by CA-MRSA, led to haematogenous spread, through the valveless system of the paranasal sinus, into the cavernous sinus, and consecutively into the brain. Similarly, Khan et al. (2000) described a case in which CA-MRSA sinusitis led to septic cavernous sinus thrombosis. The medial angle of the eye, nose and lips, known as the danger triangle of the face, also usually drains towards the cavernous sinus. This becomes clear by considering the other published cases where, for example, a concrete shrapnel injury to the nostril led to cavernous sinus thrombosis with CA-MRSA (Munckhof et al., 2008). Otitis media caused by CA-MRSA may also lead to intracranial complications. Other cases in which the CNS was infected by CA-MRSA were described in four reports of disseminated infections and five reports of brain abscesses (Table 1).

Diagnosis in our case was based on clinical investigation, medical imaging and positive blood cultures. CSF culture was sterile. In only 4/7 documented cases of CA-MRSA CNS disease, CA-MRSA was isolated from the CSF. Diagnosis in other cases was established through abscess or blood culturing (Table 1). When a primary septic cavernous sinus thrombosis is hypothesized, the absence of CA-MRSA from the CSF corresponds to the low culture positive rate (20%) of CSF in isolated septic cavernous sinus thrombosis (Ebright et al., 2001).

Because of limited therapeutic options and difficulty achieving therapeutic drug concentrations in the CSF, the treatment of MRSA causing CNS disease remains challenging. The mainstay of treatment traditionally has been vancomycin with or without rifampicin. However, in our patient, the vancomycin therapy failed, which may be attributed to its poor CSF penetration (CSF to serum ratios of only approximately 20 and 50% in patients without and with meningitis, respectively) in combination with the low levels of vancomycin in continuous infusion achieved in our patient (levels varied between 12.3 and 24.2 mg l⁻¹; normal plateau target values are from 20 to 25 mg l⁻¹). Moreover, only the free fraction (± 50%) of vancomycin is active (Dombrowski & Winston, 2008; Kessler & Kourtis, 2007). In theory, the initially low levels of free vancomycin in the CSF of our patient achieved only 0.8 – 2.0 times the vancomycin MIC of the MRSA strain. Since Lodise et al. (2008) demonstrated that patients with a MRSA bacteraemia with vancomycin MICs of ≥1.5 mg l⁻¹ only responded poorly to vancomycin, the vancomycin MIC of 1.5 mg l⁻¹ itself might also have contributed to the therapeutic failure in our case. Vancomycin is also slow-acting (Dombrowski & Winston, 2008; Kessler & Kourtis, 2007). There are sporadic case reports of the successful treatment of meningitis caused by MRSA with linezolid (Kessler & Kourtis, 2007). This may be explained in part by the excellent CSF penetration of linezolid (CSF total serum ratios of approximately 70%) (Kessler & Kourtis, 2007). It is striking that all patients with CA-MRSA CNS infection receiving linezolid (3/3) had (complete) resolution, and that in all documented cases of treatment with vancomycin without linezolid, patients had severe complications or died (7/7) (P < 0.05) (Table 1). Recently, daptomycin has also been shown to be effective. In a rabbit meningitis model, daptomycin displayed significantly superior bactericidal activity, compared with vancomycin therapy, in treating S. aureus infection (Gerber et al, 2006; Peppard et al., 2008). However, isolates of USA 300 CA-MRSA already have been described to be non-susceptible in vitro (Murthy et al., 2008). Also, dalbavancin may represent a good alternative for vancomycin, with greater tissue penetration (Peppard et al., 2008). The role of anticoagulation in septic cavernous sinus thrombosis is contentious. However, retrospective reviews of published reports indicate that haemorrhage caused by anticoagulation is rare, and that early adjunctive anticoagulation is beneficial in these patients if commenced after excluding the haemorrhagic sequelae of cavernous sinus thrombosis radiologically (Bhatia & Jones, 2002).

Although S. aureus CNS disease is well recognized, S. aureus is a rare (<5%) pathogen in community-onset meningitis (Somand & Meurer, 2009). Therefore, initial coverage for S. aureus is not warranted in this clinical setting. However, in septic cavernous sinus thromboses and brain abscesses, S. aureus is the causative agent in 60–70% of the cases, respectively (Ebright et al., 2001; Roche et al., 2003). With the advent of CA-MRSA, empirical association of an antimicrobial agent that has activity against CA-MRSA strains may prove necessary in these clinical entities. Vancomycin is already part of the empirical antimicrobial therapy for community-onset CNS infections in many parts of the world, since the increase in the prevalence of penicillin-resistant pneumococci (Van De Beek et al., 2006). Additional studies are necessary to further establish the role and adequate dosage regimens of vancomycin in the treatment of CA-MRSA CNS disease, and to compare it to agents such as linezolid.

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References

Microbicidissusis.

positive community-acquired methicillin-resistant
Staphylococcus aureus
in Egypt, April 2007.


