Fatal sepsis due to community-associated methicillin-resistant *Staphylococcus aureus* – a case report

Sepsis fatal datorat infecției cu *Staphylococcus aureus* meticilino - rezistent comunitar - prezentare de caz

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Abstract

We present the case of a community-associated methicillin-resistant Staphylococcus aureus (CA-MRSA) infection, which led to a rapidly evolving fatal sepsis with necrotizing pneumonia in a four year old girl. The patient was admitted to the Mures County Emergency Clinical Hospital at 7:50 a.m. on the 15th of March 2007. A few days before presentation the girl had suffered a minor trauma of her left heel. According to clinical, biochemical and radiological findings, septic shock with cutaneous origin, cellulitis of the left heel and bilateral pneumonia were diagnosed. She received intravenous fluid resuscitation and large spectrum antibiotic therapy was started. Later that day, the patient's condition deteriorated and she went on a cardiorespiratory stop and died at 03:25 p.m. On autopsy, bilateral necrotizing pneumonia was documented. MRSA was isolated from blood cultures. Based on epidemiological data and on phenotypical and molecular characterization, the strain was found to be a CA-MRSA harboring SCCmec type IV and Panton Valentine leukocidin genes which belonged to spa type t044. This was the first and so far only case of fatal sepsis occurring in our hospital due to CA-MRSA strain confirmed by means of molecular techniques. The dramatic rapidity of its evolution represents a major concern and demonstrates the extreme virulence and harming capacity of this type of CA-MRSA.

Keywords: *pneumonia, Panton-Valentine leukocidin, bacterial typing*

Rezumat

Prezentăm cazul unei fetițe de 4 ani care a decedat în urma unei infecții cu Staphylococcus aureus meticilino-rezistent comunitar (CA-MRSA) cu evoluție septică rapidă şi pneumonie necrotizantă. Pacienta a fost internată în Spitalul Clinic Județean de Urgență Tg. Mureş în data de 15 martie 2007, la ora 7:50. Cu câteva zile înainte a prezentat un traumatism minor la nivelul călcâiului stâng. Pe baza examenului clinic şi paraclinic, s-a stabilit diagnosticul de şoc septic de origine cutanată, celulită a călcâiului sâng şi pneumonie bilaterală. S-a instituit tratament de resuscitare hidrică şi antibiotice cu spectru larg. Starea fetiței s-a deteriorat şi a decedat la ora 15:25 în urma unui stop cardio-respirator neresuscitabil. Necropsia a evidențiat pneumonie necrotizantă bilaterală. Din hemo-

culturi, s-a izolat o tulpină MRSA. Pe baza datelor epidemiologice şi pe baza caracterelor fenotipice şi moleculare, s-a dovedit a fi o tulpină de tip comunitar: a prezentat SCCmec tip IV, a aparţinut tipului spa t044 şi a fost producătoare de leukocidina Panton-Valentin. Acesta a fost primul şi unicul caz de sepsis fatal cauzat de o tulpină MRSA comunitară confirmată prin tehnici de biologie moleculară, în spitalul nostru. Evoluţia rapidă şi fatală a infecţiei demonstrează virulenţa extremă şi capacitatea de distrucţie a acestui tip de CA-MRSA.

Cuvinte cheie: *pneumonie, leukocidina Panton-Valentine, tipizare bacteriană*

Soon after introduction of methicillin in therapy, resistance against this antibiotic appeared and methicillin-resistant *S. aureus* (MRSA) strains began their spread throughout the world. Variably present in different geographical regions, until late 1990's MRSA was mostly confined to the hospital setting. Major concern arose when the first strains occurring in outpatient population was isolated.

Compared to hospital-acquired strains, the emerging community strains presented some particularities: although resistance may be present, they are usually susceptible to several non-β-lactam antibiotics, have a faster growing rate and increased virulence due to the production of a toxin, the Panton Valentin leukocidin (PVL) (1-3). New SCC*mec* elements, designated type IV and V, different from previously known SCC*mec* elements associated with hospital-acquired MRSA strains (4,5), were described in their genetic background.

In some regions, the emerging strains became frequently encountered pathogens involved in skin infections, leading to epidemics in closed communities: day care centers, correctional facilities, army, sport teams (6-16). Although most frequently they were associated with mild or moderately severe skin and soft tissue infections, several fatal cases of bloodstream infections occurring in children and young adults were reported. In all cases, necrotizing pneumonia with rapid extension was recorded, due to production of PVL (17-20).

We present here the first case in our hospital in which a community-associated MRSA infection led to a rapidly evolving fatal sepsis with necrotizing pneumonia in a four year old girl.

BA, the sixth child of a poor family resident in the rural area nearby Odorheiu-Secuiesc (Harghita County), was admitted to the Mures County Emergency Clinical Hospital at 7:50 a.m. on the 15th of March 2007.

A few days before presentation the girl had suffered a minor trauma of her left heel. On examination at a local hospital, signs of inflammation were noticed but admission was not considered necessary. Shortly after that visit, her condition altered, the girl became feverish, cyanotic and dyspnotic, therefore she was referred to our hospital. Further details of medical history were not available.

On examination the patient looked unwell. Her temperature was not raised (37.2˚C), but an elevated pulse rate (195 beats per minute) with a regular rhythm was noticed. She had severe dyspnea and numerous bilateral rales. Her liver volume was raised. Her left foot was swollen and cellulitis was observed. Because of slight neck stiffness, consultation with an infectious disease specialist was asked for, nevertheless the diagnosis of meningoencephalitis was excluded.

Blood tests showed leukopaenia ($2.96x10^3/\mu l$) with left shift of neutrophils and trombocytopaenia ($92 \times 10^3/\mu l$). Arterial blood parameters were as follows: pH = 7.44, pO_2 = 67 mmHg, SO_2 = 93%. Biochemical examination showed increased blood urea and transaminases. Thoracic Rx showed bilateral pneumonia. Cranial and ankle CT scans were normal.

According to these findings, the following diagnoses were concluded: septic shock with cutaneous origin, cellulitis of the left heel and bilateral pneumonia.

The girl received intravenous fluid resuscitation. After blood was drawn for culture, intravenous meropenem, ciprofloxacin and teicoplanin were empirically administered.

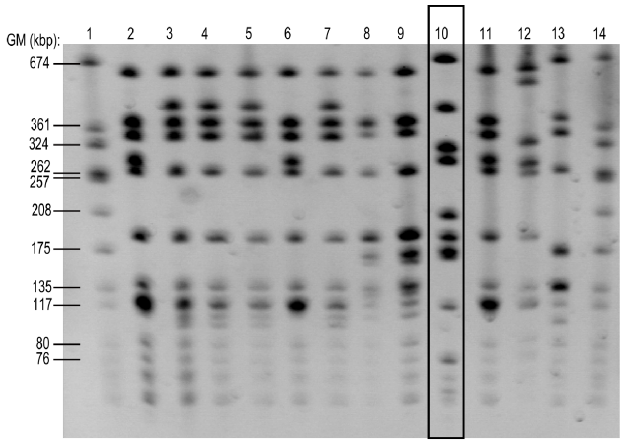

Figure 1. Macrorestriction fragments of total genome separated by pulsed-field gel electrophoresis
(lanes 1 and 14: reference strain *Staphylococcus aureus* NCTC 8325, lanes 2-9 and 11-13: clinical MRSA isolates from hospitalized patients, lane 10: MRSA strain isolated from our patient)

Later that day, her clinical status deteriorated, she became hemodinamically unstable and needed orotracheal intubation. Mechanical ventilation became very difficult, her oxygenation could not be maintained so that she entered in a severe bradycardia. She did not respond to any of the resuscitation manoeuvres and died at 03:25 p.m.

Bilateral necrotizing pneumonia was present and evidence of septic shock affecting different organs was found on autopsy. At the site of heel injury, post-mortem histological examination revealed inflammation and the presence of cocci was described.

The blood culture became positive after 10 hours of incubation and Gram-positive cocci in clusters were observed on microscopic examination. The isolated bacterium was identified as *Staphylococcus aureus*. It was PBP2a positive, proving to be MRSA. The strain was susceptible to gentamycin, erythromycin, clindamycin, ciprofloxacin, chloramphenicol, trimethoprim-sulphamethoxazole, vancomycin, teicoplanin and linezolid and resistant to kanamycin and tetracyclin.

Our initial suspicion that we faced a case of severe infection due to a community-associated MRSA (CA-MRSA), based on epidemiological data and the unusual susceptibility of the strain, was reinforced by the fact that PFGE (pulsed field gel electrophoresis) typing revealed a pulsotype different from those known in our collection of hospital-acquired MRSA strains (*Figure 1*).

Later, the strain was further characterized by testing for the presence of *luk*S-*luk*F-PV gene responsible of PVL toxin production, spa and SCC*mec* typing. These tests confirmed the strain to be a CA-MRSA that harbored SCC*mec* type IV. It presented the *luk*S-*luk*F-PV gene and belonged to *spa* type t044.

The *spa* type t044 is a widespread European clone known as a CA-MRSA strain most frequently associated with sequence type ST80 belonging to clonal complex CC044. As reported by SeqNet.org, it accounts for 2.5% of all circulating MRSA strains (21). In some regions of Europe it is one of the most common clonal types of CA-MRSA beside t019/ST30-IV and t008/ST8-IV (USA300) (22). Although the presence of this *spa* type in Romania was already reported (23-25), it was the first case when its involvement in fatal sepsis associated with necrotizing pneumonia in a child was documented.

The vast majority of MRSA infections encountered in our hospital, which followed the typical pattern of hospital acquired infections, were caused by MRSA strains belonging to a single clonal cluster, reflecting intrahospital transmission (26). No strain showing identical PFGE pattern with the strain presented in this report had been seen before, nor since then in our collection

of hospital strains. Nevertheless, a strain isolated from a wound swab collected in ambulatory presented a genomic similarity of 92%, but further characterisation of this strain in respect to SCC*mec* and *spa* type was not performed.

In a previous study we have undertaken an evaluation of MRSA nasal colonisation of children attending kindergartens in Tg. Mures and we have found a rate of colonisation of 2,5% (27). None of the recovered strains were similar to the one described in this case report.

CA-MRSA strains have some phenotypic traits upon which CA-MRSA can be assumed: these strains are usually susceptible to non-beta-lactam antibiotics since on the short SCC*mec* type IV or V cassettes are not carried additional resistance genes. However, the acquisition of resistance mechanisms unrelated to SCC*mec* during their evolution already rendered several CA-MRSA strains resistant to different classes of antibiotics.

One of the most important phenotypic features of CA-MRSA is the production of the Panton-Valentin leukocidin. This exotoxin is variably present in *S. aureus* strains, but it was detected at a high frequency in CA-MRSA (19). PVL is encoded by contiguously located cotranscribed genes, *luk*S-PV and *luk*F-PV. Their gene products assemble as hetero-heptamers and synergistically display cytolytic pore-forming activity specifically directed at the cell membrane (28). As injecting PVL into the skin of rabbits causes dermal necrosis, it is assumed that this toxin plays a role in the severity of skin and skin-structure infections in humans (29, 30).

In conclusion, this was the first and so far unique case of community onset fatal sepsis occurring in our hospital due to CA-MRSA strain confirmed by means of molecular techniques. The dramatic rapidity of evolution represents a major concern and demonstrates the extreme virulence and harming capacity of this type of CA-MRSA.

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References

1. Bocchini CE, Hulten KG, Mason EO, Gonzalez BE, Hammerman WA, Kaplan SL: Panton-Valentin leukocidin genes are associated with enhanced inflammatory respons and local disease in acute hematogenous Staphylococcus aureus osteomyelitis in children. Pediatrics, 2006, 117:433-440.
2. Naimi TS, LeDell K, Como-Sabetti K, Borchardt SM, Boxrud DJ, Etienne J et al: Comparison of community- and health care-associated methicillin-resistant Staphylococcus aureus. JAMA, 2003, 290:2976-2984.
3. Hallin M, Denis O, Deplano A, de Ryck R, Crevecoeur S, Rottiers S et al: Evolutionary relationship between sporadic and epidemic strains of healthcare-associated methicillin-resistant Staphylococcus aureus. Clin Microbiol Infect, 2008, 14:659-669.
4. Ma XX, Ito T, Tiensasitorn C, Jamklang M, Chongtrakool P, Boyle-Vavra S et al: Novel type of SCCmec identified in community-associated methicillin-resistant Staphylococcus aureus. Antimicrob Agents Chemother, 2002, 46:1147-1152.
5. Ito T, Ma XX, Takeuchi F, Okuma K, Yuzawa H, Hiramatsu K: Novel type V staphylococcal chromosome cassette mec driven by a novel cassette chromosome recombinase, ccrC. Antimicrob Agents Chemother, 2004, 48:2637-2651.
6. MMRW Report: Methicillin resistant Staphylococcus aureus skin and soft tissue infections in a state prison – Mississippi, 2000. MMWR Morb Mortal Wkly Rep, 2001, 50:919-922.
7. MMRW Report: Methicillin-resistant Staphylococcus aureus infection among competitive sports participants – Colorado, Indiana, Pennsylvania and Los Angeles county 2000-2003. MMWR Morb Mortal Wkly Rep, 2003, 52:793-795.
8. MMWR Report: Community-associated methicillin-resistant Staphylococcus aureus infections in Pacific Islanders, Hawaii 2001-2003. MMWR Morb Mortal Wkly Rep, 2004, 53:767-770.
9. Boubaker K, Diebold P, Blanc DS, Vandenesch F, Praz G, Dupuis G et al: Panton-Valentine leukocidin and staphylococcal skin infection in schoolchildren. Emerg Infect Dis, 2004, 10:121-124.
10. Baggett HC, Hennessy TW, Rudolph K, Bruden D, Reasonover A, Parkinson A, et al: Community-onset methicillin-resistant Staphylococcus aureus associated with antibiotic use and the cytotoxin Panton-Valentin Leukocidin during a furunculosis outbreak in rural Alaska. J Infect Dis, 2004, 189:1565-1673.
11. Begier EM, Frenette K, Barrett NL, Mshar P, Petit S, Boxrud DJ et al: A high-morbidity outbreak of methicillin-resistant Staphylococcus aureus among players on a college football team, facilitated by cosmetic body shaving and turf burns. Clin Infect Dis, 2004, 39:1446–53.

12. Kaplan SL, Hulten KG, Gonzalez BE, Hammerman WA, Lamberth L, Versalovic J et al: Three-year surveillance of community-acquired Staphylococcus aureus infections in children. Clin Infect Dis, 2005; 40:1785–91.
13. Moran GJ, Amii RN, Abrahamian FM, Talan DA: Methicillin-resistant Staphylococcus aureus in community acquired skin infections. Emerg Infect Dis, 2005, 11: 928
14. Mulvey MR, Chui L, Ismail J, Murphy C, Chang N, Alfa M: Development of a Canadian standardized protocol for subtyping methicillin-resistant Staphylococcus aureus using pulsed-field gel electrophoresis. J Clin Microbiol, 2001, 39:3481-3485.
15. Ochoa TJ, Mohr J, Wanger A, Murphy JR, Heresi GP: Community-associated methicillin-resistant Staphylococcus aureus in Pediatric Patients. Em Infect Dis, 2005, 11:966-968.
16. Fridkin SK, Hageman JC, Morrison M, Sanza LT, Corno-Sabetti K, Jernigan JA et al: Methicillin-resistant Staphylococcus aureus disease in three communities. N Engl J Med, 2005, 352:1436-1444.
17. MMWR report: Four pediatric deaths from coommunity-acquired methicillin-resistant Staphylococcus aureus – Minnesota and North Dakota, 1997-1999. MMWR Morb Mortal Wkly Rep, 1999, 48:707-710.
18. Dufour P, Gillet Y, Bes M, Lina G, Vandenesch F, Floret D et al: Community-acquired methicillin-resistant Staphylococcus aureus infections in France: emergence of a single clone that produces Panton-Valentine Leukocidin. Clin Infect Dis, 2002, 35.819-824.
19. Vandenesh F, Naimi T, Enright MC, Lina G, Nimmor GR, Heffernan H et al: Community-acquired methicillin-resistant Staphylococcus aureus carrying Panton-Valentine leukocidin genes: worldwide emergence. Emerg Infect Dis, 2003, 9:978-984
20. Francis JS, Doherty MC, Lopatin U, Johnston CP, Sinha G, Ross T et al: Severe community-onset pneumonia in healthy adults caused by methicillin-resistant Staphylococcus aureus carrying the Panton-Valentine leukocidin genes. Clin Infect Dis, 2005, 40:100–7.
21. Friedrich AW, Witte W, de Lencastre H, Hryniewitz W, Scheres J, Westh H: A European laboratory network for sequence-based typing of methicillin-resistant Staphylococcus aureus (MRSA) as a communication platform between human and veterinary medicine – an update on Sequence.org, Eurosurveillance, 2008, 13:1-5.
22. Bartels MD, Boye K, Larsen AR, Skov R, Westh H: Rapid increase of geneticvally diverse methicillin-resistant Staphylococcus aureus, Copenhagen, Denmark. Emerg Infect Dis, 2007, 13:1533-1540.
23. Oprea M, Codița I, Coldea L, Drăgulescu EC, Stăuț M: Characterization of Staphylococcus aureus strains isolated in Romania in intensive care units in January 2006 – April 2007 interval. 5th Balkan Congress of Microbiology, "Microbiologia Balkanica 2007", 24-27 October, 2007, Budva, Montenegro.
24. Oprea M, Drăgulescu EC, Coldea IL, Codița I, Szmal C, Străuț, M: Molecular characterization of Staphylococcus aureus isolates belonging of to most prevalent spa-types recovered from Romanian hospitals during 2006-2007. 18th European Conference of Clinical Microbiology and Infectious Diseases, 19-22 April, 2008, Barcelona, Spain, P1436.
25. Ionescu R, Mediavilla JR, Grigorescu DO, Idomir M, Kreiswirth BN, Roberts RB: Analiza epidemiologică, utilizând tehnici de biologie moleculară, a transmiterii tulpinilor de Staphylococcus aureus meticilino-rezistent în Spitalul Clinic Județean de urgență Brașov. National Conference on Microbiology and Epidemiology, October 2009, Brasov, Romania.
26. Székely E, Lőrinczi L, Bilca D, Földes A, Voidazean S: Staphylococcus aureus involved in bacteraemia in an emergency hospital. 1st RAML Congress June 2009, Targu Mures, abstract in: Romanian Review of Laboratory Medicine, 2009, 15(2suppl): 43.
27. Székely E, Bucur G, Bilca D, Földes A, Jákó Zs, Sabău M et al: Methicillin-resistant Staphylococcus aureus colonization in the community: incidence, phenotypic and molecular characteristics. 4th RAML Conference 18-21 June 2008, Cluj Napoca, abstract in: Romanian Review of Laboratory Medicine, 2009, 11(2suppl): 35-36.
28. Kaneko J, Kamio Y: Bacterial two-component and hetero-heptameric pore-forming cytolytic toxins structures, pore-forming mechanisms and organization of genes. Biosci Biotechnol Biochem, 2004, 68: 981-1003.
29. Deresinski S: Methicillin-resistant Staphylococcus aureus: an evolutionary, epidemiologic and therapeutic odyssey. Clin Infect Dis, 2005, 40:562-563.
30. Labandeira-Rey M, cuzon F, Boisset S, Brown BL, Bes M, Benito Y et al : Staphylococcus aureus Panton-Valentine leukocidin causes necrotizing pneumonia. Science, 2007, 315:1130-1133