A Case of Rapidly Progressive Necrotizing Pneumonia Caused by Community-Acquired Methicillin-Resistant *Staphylococcus aureus*

Robert P Dickson MD, Shay M Martinez MD, and Justin R Ortiz MD

We present the case of a patient with a necrotizing multilobar pneumonia caused by community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA). The patient presented with shortness of breath and a productive cough of 3 days duration. On arrival to the emergency department she was intubated for increased work of breathing and given vasopressors for hypotension refractory to fluid resuscitation. Blood cultures taken at admission, sputum cultures from the patient's endotracheal tube, and bronchoalveolar lavage cultures all grew *S. aureus* resistant to penicillinase-resistant penicillins. Over the following days the patient's respiratory function deteriorated as she grew progressively hypoxemic and hypercarbic despite aggressive mechanical ventilation and intravenous antibiotics. On day 4 of her hospitalization a computed tomogram revealed extensive pulmonary necrosis consistent with necrotizing pneumonia. The patient's family elected to withdraw support, and the patient rapidly died following cessation of mechanical ventilation. *Key words: pneumonia, bacterial, Staphylococcus aureus, respiratory insufficiency, methicillin-resistant Staphylococcus aureus, MRSA*. [Respir Care 2008;53(9):1223–1226. © 2008 Daedalus Enterprises]

Introduction

Necrotizing pneumonia caused by community-acquired methicillin-resistant *Staphylococcus aureus* (community-acquired MRSA) has been reported with increasing frequency.[1-7] Providers should recognize that necrotizing pneumonia caused by community-acquired MRSA can present without fever or hemoptysis and can be rapidly progressive and fatal.

Case Reports

A 63-year-old woman presented with shortness of breath and cough to a community emergency department. The patient reported that she had felt ill with a cough and myalgias for the prior 2 weeks. Her dyspnea worsened and her cough progressed with the development of productive green/yellow sputum in the 3 days prior to presentation. She denied hemoptysis or fever. She called paramedics to her home and was found to be tachypneic, hypotensive (blood pressure 78/58 mm Hg), and with a temperature of 35.5°C. A chest radiograph revealed left-upper-lobe and right-lower-lobe consolidations with air bronchograms that suggested multifocal pneumonia (Fig. 1). She was intubated because of perceived increased work of breathing, and she received roughly 9 L of crystalloid (normal saline and lactated Ringer's solution), but she remained hypotensive, and a norephinephrine infusion was begun. She received intravenous ceftriaxone and azithromycin for presumed community-acquired pneumonia. She was admitted to the intensive care unit (ICU).

Her medical history was notable for several prior admissions for bronchitis and pneumonia, a 40-pack-year smoking history, and normal pulmonary function tests performed 4 months prior to this presentation. She also had hypertension, hyperlipidemia, diet-controlled diabetes mellitus, bipolar disorder, and allergic rhinitis. Her last hospitalization was 8 months prior to this presentation for community-acquired pneumonia. She volunteered regularly in a community homeless shelter.

Robert P Dickson MD and Shay M Martinez MD are affiliated with the Department of Medicine; Justin R Ortiz MD is affiliated with the Division of Pulmonary and Critical Care Medicine, Department of Medicine, Harborview Medical Center, University of Washington, Seattle, Washington.

The authors report no conflicts of interest related to the content of this paper.

Correspondence: Robert P Dickson MD, Department of Medicine, University of Washington Medical Center, 4245 Roosevelt Way NE, Seattle Washington 98105-6920. E-mail: rpd4@u.washington.edu.

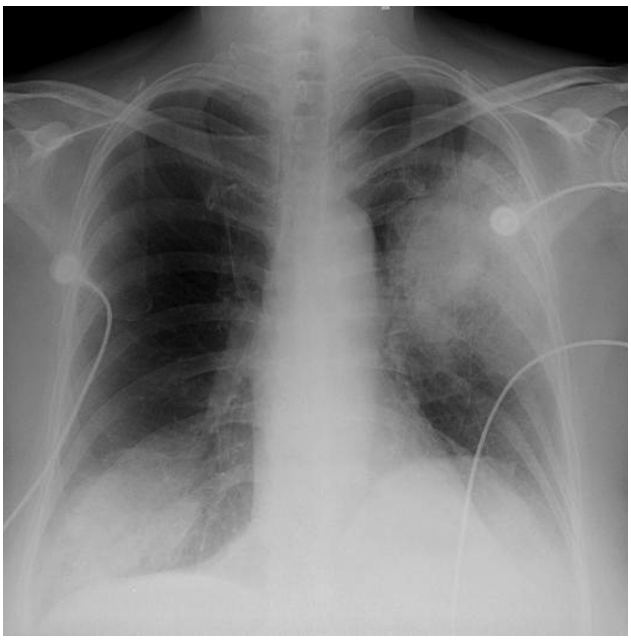

Fig. 1. Portable chest radiograph taken on presentation to the emergency department, prior to intubation. There are consolidations and air bronchograms in the right-lower and left-upper lobes, which suggests multilobar pneumonia.

Physical examination on admission to the ICU revealed a sedated, intubated, and afebrile woman with diffuse rhonchi and both inspiratory and expiratory wheezing. Initial endotracheal tube (ETT) suctioning revealed green/yellow secretions but no blood. Initial screening laboratory tests revealed a slightly elevated white-blood-cell count (10.9×10^9/L), an arterial lactate of 3.1 mmol/L, and an elevated creatinine of 3.7 mg/dL.

In the ICU, her mechanical ventilation settings were per the Acute Respiratory Distress Syndrome Network's lung-protective ventilation protocol. She initially required a fraction of inspired oxygen of 0.60 and positive end-expiratory pressure of 10 cm H_2O for adequate oxygenation. We changed her antibiotics to intravenous piperacillin-tazobactam and azithromycin for empirical coverage of common community-acquired pneumonia pathogens, atypical bacteria, and resistant Gram-negative rods.

On ICU day 2 her blood pressure stabilized and vasopressors were discontinued. A blood culture collected in the emergency department on admission and sputum culture both grew *S. aureus*, and intravenous vancomycin was added. The cultured organism was resistant to penicillinase-resistant penicillins but sensitive to macrolides, quinolones, linezolid, clindamycin, and vancomycin. We tested for inducible clindamycin resistance, which was absent. Subsequent pulsed-field gel electrophoresis revealed the organism to be an isolate of USA300, which is one of the 2 predominant MRSA clones responsible for North American community-acquired MRSA infections.[8] She underwent a bronchoscopy for a research trial in which she was enrolled. Bronchoscopy revealed no bleeding, but marked erythema of the distal left mainstem and lobar segments. She grew transiently neutropenic, though her neutrophil count recovered and was within normal limits within 12 hours.

On day 3 of hospitalization she remained afebrile but began to require a higher fraction of inspired oxygen and positive end-expiratory pressure for oxygenation. Chest radiograph revealed worsening of the lobar consolidations, along with lucencies that suggested possible cavitations in her left-upper lung fields. Bronchoalveolar lavage fluid collected on day 2 grew MRSA in culture. Given the absence of any other cultured organism, we narrowed the antibiotic regimen to intravenous vancomycin alone. On day 4 of hospitalization her oxygenation continued to deteriorate. Suctioning of the ETT began to return reddish-brown sputum. Given the patient's worsening pulmonary function, bloody sputum, and the suggestion of cavitations on her chest radiograph, she underwent computed tomography, which revealed extensive pulmonary necrosis consistent with necrotizing pneumonia, worse diffusely in both lobes of the left lung and in the right lung base (Fig. 2). As such lesions would prove refractory to intravenous antibiotics, we requested a thoracic surgery consult. The surgeons' assessment was that the patient had no realistic options for a surgical intervention, as she would require a left pneumonectomy and a right-lower lobectomy as surgical treatment for the necrotizing pneumonia. Informed of her worsening clinical situation, the patient's family elected to withdraw support. Palliative care measures were instituted, the ETT was removed, and she rapidly died.

Discussion

This patient's presentation was notable only for shortness of breath, cough, and focal opacities on chest radiograph. Within 4 days of admission her disease had progressed to an irreversible necrotizing process and her oxygenation became unstable despite mechanical ventilation.

In 2002, 16 cases of necrotizing pneumonia caused by community-acquired MRSA were reported in immunocompetent patients.[7] The described clinical course was often characterized by respiratory viral prodrome, tachycardia, hemoptysis, pleural effusions, and leucopenia. The in-hospital mortality rate among those patients was 75%. Since that report the frequency of case reports of community-acquired-MRSA-caused necrotizing pneumonia has risen.[1-7] The Panton-Valentine leukocidin virulence factor, first described in 1932,[9] has been implicated as the feature of community-acquired MRSA that makes its pneumonia more aggressive, necrotizing, and fatal than that of methicillin-sensitive *Staphylococcus aureus* or hospital-acquired

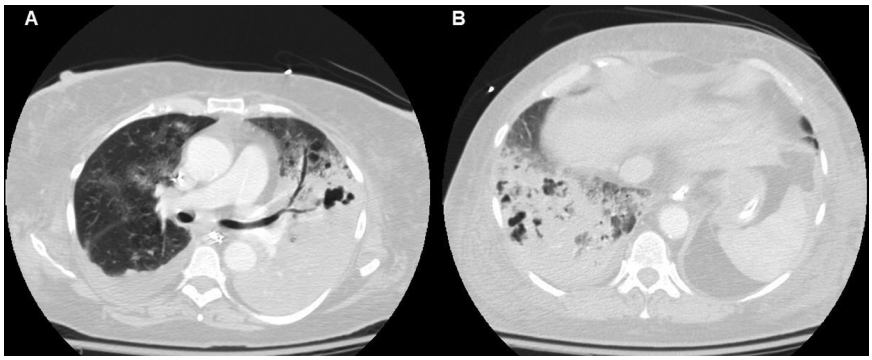

Fig. 2. Chest computed tomogram with contrast obtained on day 4 of admission. A: The left lung has diffuse consolidation, air bronchograms, and areas of cavitation. There is a right-sided pleural effusion. B: The right lung base has consolidation and areas of cavitation.

MRSA.[5,7] Recently, strains of *S. aureus* with the Panton-Valentine leukocidin virulence factor were shown to cause necrotizing pneumonia in a murine model.[10]

No consensus exists regarding the definition of infections caused by community-acquired MRSA. Since 2000 the Centers for Disease Control and Prevention has used an epidemiologically-based definition that defines community-acquired MRSA specimens as those recovered no more than 48 hours after hospitalization and from a patient without a history of hospitalization, surgery, dialysis, residence in long-term-care facility within the past 12 months, prior MRSA infection, or indwelling devices.[11] Recently Millar et al called for a definition based instead on microbiological and molecular characterization of the pathogen.[12]

Our patient's MRSA did not meet the Centers for Disease Control epidemiologic criteria for community-acquired MRSA, because she was briefly hospitalized 8 months prior to presenting to us. Yet microbial analysis argues strongly that her isolate should be considered community-acquired MRSA. The MRSA grown from our patient's blood, sputum, and bronchoalveolar lavage fluid was resistant to penicillinase-resistant penicillins but sensitive to macrolides, quinolones, linezolid, clindamycin, and vancomycin; this sensitivity pattern is characteristic of community-acquired MRSA and distinct from that of hospital-acquired MRSA, which typically exhibits resistance to numerous agents other than penicillinase-resistant penicillins.[6,7,13,14] Pulsed-field gel electrophoresis of the patient's sputum culture revealed the MRSA to be the USA300 MRSA clone, which has been a major cause of community-acquired MRSA infections but not of hospital-acquired MRSA infections.[8] This case illustrates both the challenge of defining community-acquired MRSA infection and the limitations of using strictly epidemiologically based definitions for diseases caused by genetically distinct organisms.

Our patient's presentation was typical of prior reports of community-acquired MRSA necrotizing pneumonia in that she reported a 2-week viral respiratory prodrome prior to rapid deterioration of her respiratory function. She was not tested for respiratory virus infection; however, influenza, influenza-like illness, and respiratory syncytial virus activity are historically at very low levels in Seattle during July.

It is unclear whether this prodrome period reflects the indolent early stages of staphylococcal infection or if a separate preceding viral infection predisposes to subsequent staphylococcal infection. Patients with community-acquired MRSA pneumonia who lack this prodrome have been reported to have better clinical outcomes, and it has been hypothesized that the pulmonary microbial burden is lower in those who lack an initial viral pulmonary insult.[15]

Homelessness has been proposed to be a risk factor for contraction of community-acquired MRSA infection, specifically of the USA300 strain found in our patient's blood and sputum.[16] Though our patient was not homeless, she volunteered regularly in a homeless shelter and may have contracted MRSA there.

Our patient lacked the presenting complaint of hemoptysis typical of most prior reports of community-acquired MRSA necrotizing pneumonia, and the bronchoscopy found no evidence of hemorrhage. Within 48 hours of that bronchoscopy, however, reddish-brown sputum was suctioned from the ETT and computed tomography revealed diffuse cavitations and necrosis. She was also afebrile at presentation and throughout her ICU course, which might reflect her advanced age and inability to mount a robust inflammatory response. This case illustrates how rapidly this process can evolve, even in an immunocompetent patient with only focal opacities on her presenting chest radiograph and a relatively benign-appearing bronchoscopy. This case also demonstrates that the absence of hemoptysis and fever should not preclude consideration of community-acquired MRSA as a potential pneumonia pathogen.

Multiple authors have speculated that the leukopenia observed in this disease may be mediated directly by Pan-

ton-Valentine leukocidin, which is an exotoxin that directly lyses neutrophils.[7,10,13] Though our patient presented with a normal neutrophil count, she quickly grew leukopenic. Nevertheless, her leukocyte count rose from the nadir on day 2 of admission and she quickly developed a leukocytosis (18.0×10^9/L and rising at the time of her death). Though leukopenia has been described as an ominous prognostic factor in necrotizing community-acquired MRSA pneumonia,[17] our patient's clinical situation worsened as her leukocyte count rose. It is possible that the white-blood-cell count is a rough, inverse biomarker of the Panton-Valentine leukocidin burden, though this correlation is purely speculative. Community-acquired MRSA contains other toxins, including toxic shock syndrome toxin 1.

Our patient's clinical course deteriorated despite intravenous azithromycin and vancomycin, to which the pathogen was susceptible in vitro. Other antibiotics to which the organism was susceptible, including linezolid, levofloxacin, clindamycin, and trimethoprim/sulfamethoxazole, were considered but not administered. The patient did not receive antistaphylococcal therapy until the second day of her hospitalization; this illustrates the importance of not overlooking community-acquired MRSA among the potential pathogens on presentation. When patients present with risk factors for community-acquired MRSA, such as this patient's history of volunteering in a homeless shelter, vancomycin should be considered as empirical antibiotic therapy.

Commercially available intravenous immune globulin, which has in vitro activity against Panton-Valentine leukocidin,[18] is another treatment alternative that was not used. By the time the diagnosis of necrotizing pneumonia is made, the pathology achieved by community-acquired MRSA and Panton-Valentine leukocidin is advanced, and it may be difficult to neutralize the organism and its virulence factor. A vaccine against Panton-Valentine leukocidin has been proposed and is biochemically plausible.[13] Absent microbiological data, organisms to consider based on the presence of necrotizing findings on chest imaging include anaerobes, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, Nocardia, and Actinomyces.

Prompt diagnosis and intervention may be critical in improving outcomes of necrotizing pneumonia due to community-acquired MRSA. We recommend considering community-acquired MRSA among pathogens that cause community-acquired pneumonia, even in an afebrile patient with a normal white-blood-cell count and without hemoptysis, especially if the patient does not respond appropriately to initial management.

REFERENCES

1. Castaldo ET, Yang EY. Severe sepsis attributable to community-associated methicillin-resistant *Staphylococcus aureus*: an emerging fatal problem. Am Surg 2007;73(7):684-687.
2. Vayalumkal JV, Whittingham H, Vanderkooi O, Stewart TE, Low DE, Mulvey M, et al. Necrotizing pneumonia and septic shock: suspecting community-acquired MRSA in patients presenting to Canadian emergency departments. CJEM 2007;9(4):300-303.
3. Garnier F, Tristan A, Francois B, Etienne J, Delage-Corre M, Martin C, et al. Pneumonia and new methicillin-resistant *Staphylococcus aureus* clone. Emerg Infect Dis 2006;12(3):498-500.
4. Monaco M, Antonucci R, Palange P, Venditti M, Pantosti A. Methicillin-resistant *Staphylococcus aureus* necrotizing pneumonia. Emerg Infect Dis 2005;11(10):1647-1648.
5. 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(1):100-107.
6. 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(7):819-824.
7. Gillet Y, Issartel B, Vanhems P, Fournet JC, Lina G, Bes M, et al. Association between *Staphylococcus aureus* strains carrying gene for Panton-Valentine leukocidin and highly lethal necrotising pneumonia in young immunocompetent patients. Lancet 2002;359(9308):753-759.
8. Diep BA, Gill SR, Chang RF, Phan TH, Chen JH, Davidson MG, et al. Complete genome sequence of USA300, an epidemic clone of community-acquired meticillin-resistant *Staphylococcus aureus*. Lancet 2006;367(9512):731-739.
9. Panton P, Valentine F. Staphylococcal toxin. Lancet 1932;1:506-508.
10. Labandeira-Rey M, Couzon F, Boisset S, Brown EL, Bes M, Benito Y, et al. *Staphylococcus aureus* Panton-Valentine leukocidin causes necrotizing pneumonia. Science 2007;315(5815):1130-1133.
11. Fridkin SK, Hageman JC, Morrison M, Sanza LT, Como-Sabetti K, Jernigan JA, et al. Methicillin-resistant *Staphylococcus aureus* disease in three communities. N Engl J Med 2005;352(14):1436-1444.
12. Millar BC, Loughrey A, Elborn JS, Moore JE. Proposed definitions of community-associated meticillin-resistant *Staphylococcus aureus*. J Hosp Infect 2007;67(2):109-113.
13. Boyle-Vavra S, Daum RS. Community-acquired methicillin-resistant *Staphylococcus aureus*: the role of Panton-Valentine leukocidin. Lab Invest 2007;87(1):3-9.
14. Bradley SF. *Staphylococcus aureus* pneumonia: emergence of MRSA in the community. Semin Respir Crit Care Med 2005;26(6):643-649.
15. Alonso-Tarres C, Villegas ML, de Gispert FJ, Cortes-Lletget MC, Rovira Plarromani A, Etienne J. Favorable outcome of pneumonia due to Panton-Valentine leukocidin-producing *Staphylococcus aureus* associated with hematogenous origin and absence of flu-like illness. Eur J Clin Microbiol Infect Dis 2005;24(11):756-759.
16. Gilbert M, MacDonald J, Gregson D, Siushansian J, Zhang K, Elsayed S, et al. Outbreak in Alberta of community-acquired (USA300) methicillin-resistant *Staphylococcus aureus* in people with a history of drug use, homelessness or incarceration. CMAJ 2006;175(2):149-154.
17. Gillet Y, Vanhems P, Lina G, Bes M, Vandenesch F, Floret D, et al. Factors predicting mortality in necrotizing community-acquired pneumonia caused by *Staphylococcus aureus* containing Panton-Valentine leukocidin. Clin Infect Dis 2007;45(3):315-321.
18. Gauduchon V, Cozon G, Vandenesch F, Genestier AL, Eyssade N, Peyrol S, et al. Neutralization of *Staphylococcus aureus* Panton-Valentine leukocidin by intravenous immunoglobulin in vitro. J Infect Dis 2004;189(2):346-353.