Critical Pneumonia Complicating Early-Stage Pregnancy

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We present a case of community-acquired methicillin-resistant *Staphylococcus aureus* necrotizing pneumonia, Panton-Valentine leukocidin positive, in a woman at 14 weeks of pregnancy. To our knowledge, this is the first case reporting this critical lung infection occurring during an early phase of pregnancy. This case study alerts physicians to the increasing worldwide spread of these uncommon yet virulent and potentially lethal infections. In our patient, antibiotic therapy with linezolid plus rifampin started at 14 weeks of pregnancy had a successful outcome without inducing toxicity or teratogenesis in the fetus. (Anesth Analg 2010;110:852–4)

Community-acquired (CA) pneumonia (CAP) and influenza are the eighth leading cause of death in the United States and increased significantly from 2004 to 2005.[1] About 10% of all cases of CAP are caused by *Staphylococcus aureus*; compared with rates reported in the last 2 decades of the 20th century, the incidence of *S aureus* pneumonia increased by 200% from 2001 to 2003. This epidemiologic change is associated with the worldwide emergence of methicillin-resistant *S aureus* (MRSA) isolates from community infections.[2] CA-MRSA strains mainly cause skin and soft-tissue infections, but some reports describe severe, life-threatening diseases.[3] CA-MRSA strains are less resistant than hospital-acquired MRSA strains to non–β-lactam antibiotics, but they are more virulent and strongly associated with genes encoding the exotoxin Panton-Valentine leukocidin (PVL).

We report a case of a PVL-positive CA-MRSA necrotizing pneumonia in a previously healthy 21-year-old woman who was 14 weeks pregnant.

CASE DESCRIPTION

A previously healthy 21-year-old woman who was 14 weeks (after the last menstrual period) pregnant came to our emergency room with a 3-day history of influenza-like symptoms. Physical examination on admission disclosed normal temperature and arterial blood pressure but tachypnea and tachycardia. Routine inflammatory indices disclosed a normal white blood cell (WBC) count (6100 cells/mm^3), increased polymorphonuclear cells (88.7%), and increased ultrasensitive C-reactive protein (28.8 mg/dL). A chest radiograph showed multiple, bilateral infiltrates. On day 2, the WBC count decreased to 1500 and her temperature increased to 39.3°C. Blood and sputum specimens were sampled for cultures. Assays for causative microorganisms included polymerase chain reaction for *Mycobacterium tuberculosis*, human immunodeficiency virus antibodies, indirect fluorescent-antibody stain for *Pneumocystis carinii*, urinary antigens for *Legionella*, herpes virus, cytomegalovirus, and pneumotropic virus antibodies. CAP was diagnosed and empirically treated with amoxicillin/clavulanic acid and clarithromycin. On day 3, the patient had hemoptysis and increasing dyspnea. A second chest radiograph disclosed worsening pneumonia, with foci coalescing into large consolidations with cavitary lung lesions (Fig. 1). Pulmonary tuberculosis was suspected and empirically treated, without discontinuing β-lactam/macrolide therapy. However, the patient's condition continued to deteriorate, and on day 5, she was transferred to the intensive care unit. On arrival to the intensive care unit, the patient had severe dyspnea, hypoxemia, hypotension, and tachycardia. The patient was then sedated, tracheally intubated, and placed on mechanical ventilation. Fiberoptic bronchoscopy showed an ulcerated, friable mucosa. Sputum and bronchoalveolar lavage (BAL) specimens were negative for alcohol-acid resistant bacilli and, although the polymerase chain reaction was still unavailable, because necrotizing staphylococcal pneumonitis was suspected, antibiotics were suspended, and empirical antimicrobial therapy was started with linezolid 600 mg twice daily and rifampin 300 mg every 8 hours.

Three days later, sputum and BAL isolates confirmed an MRSA luk-PVL–positive infection resistant to β-lactam antibiotics. Five days after linezolid/rifampin therapy began, a control BAL specimen was negative for MRSA infection. The patient completed a 4-week course of linezolid/rifampin. A healthy newborn baby was delivered by cesarean delivery at 40 weeks' gestation. The patient gave consent to publication of her case.

The *S aureus* strain isolated was a USA300 CA-MRSA clone carrying staphylococcal cassette chromosome *mec* type IV and the genes encoding PVL. The isolate was resistant to oxacillin but susceptible to macrolides, fluoroquinolones, aminoglycosides, linezolid, rifampin, vancomycin, teicoplanin, tetracyclines, and trimethoprim plus sulfamethoxazole.

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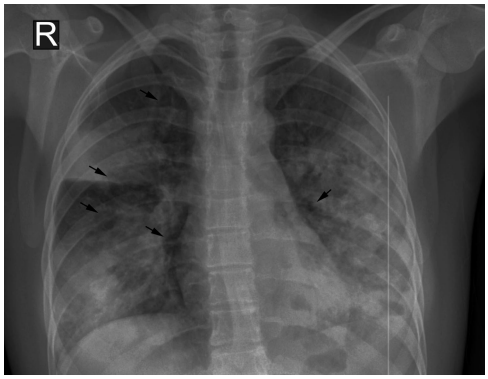

Figure 1. Chest radiograph on day 3 showing bilateral cavitary lung lesions (black arrows).

DISCUSSION

Life-threatening CA-MRSA PVL-positive necrotizing pneumonia in a pregnant woman is a distinctly unusual event. To our knowledge, no other similar cases have been reported at this early stage of pregnancy. Recently, 1 case of a CA-MRSA PVL-positive pneumonia was described in a woman at 32 weeks of pregnancy who underwent a cesarean delivery after admission and was successfully treated with linezolid plus rifampin antibiotic therapy.[4]

The high rate of mortality associated with these infections explains why consensus recommends aggressive antibiotic treatment when CA-MRSA pneumonia is suspected.[5]

When choosing appropriate antibiotics, one should consider potential toxic and teratogenic effects. Subinhibitory concentrations of antibiotics interfere with several virulence factors, including phagocytosis, adherence, and toxin production.[6] In our patient, although the isolated MRSA was susceptible to vancomycin and teicoplanin, the drugs do not modulate *S aureus* α-toxin expression,[5] and vancomycin at conventional doses does not sufficiently penetrate the lung tissue to kill MRSA.[7] The microorganism was also susceptible to clindamycin, which strongly reduces α-toxin gene expression, toxic shock syndrome toxin-1, and exfoliative toxin production.[6] One of our concerns was possible drug-induced clindamycin resistance.[5] A final reason for deciding against these drugs was their "undetermined teratogenic risk."[8] Another therapeutic option was fluoroquinolones, antibiotics that are considered "unlikely to increase the risk of teratogenicity."[8] We also preferred not to use these drugs because of reported plasmid-mediated quinolone resistance and their unclear effect on toxin production.[5] Although trimethoprim/sulfamethoxazole is not associated with an increased teratogenic risk, the drug competes with folic acid, and its use is discouraged during pregnancy.[8] Aminoglycosides are potentially associated with an increased incidence of irreversible damage in the human fetus.[8] Conversely, because the MRSA isolated in our patient was also susceptible to linezolid, we finally decided to use this drug in line with the American Thoracic Society's therapeutic guidelines for CA-MRSA PVL-positive pneumonia.[5] In a study testing several subinhibitory concentrations, at minimum inhibitory concentration, linezolid reduced the secretion of several virulence factors.[9] The drug also acts by switching off toxin production.[6] Linezolid concentrates in lung epithelial lining fluid, maintaining a concentration larger than the minimum inhibitory concentration required to inhibit the growth of 90% of organisms of MRSA throughout the dosing

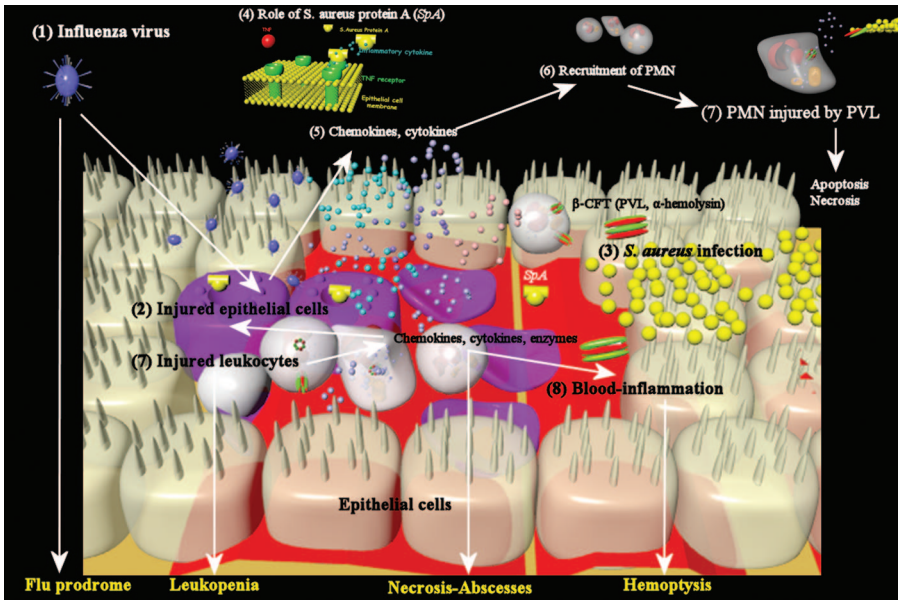

Figure 2. The airway epithelium war. The sequence of events occurring over the pulmonary epithelium leading to the main clinical manifestations (yellow) of methicillin-resistant *Staphylococcus aureus* (MRSA) Panton-Valentine leukocidin (PVL)-positive necrotizing pneumonia. Events start with an influenza-like infection (1) (flu-prodrome), which damages the epithelial cells (2), making them more exposed to MRSA infection (3) (MRSA has tropism for injured airway epithelium). MRSA releases β-channel pore-forming toxins (β-CFTs), including PVL and α-hemolysin. PVL acts as a positive regulator of protein A, a substance that binds to the tumor necrosis factor-α receptor of the epithelial cell (4). The injured airway epithelium releases chemokines and cytokines (5) recruiting polymorphonuclear (PMN) cells (6). PMN cells infiltrate the epithelium and are attacked by the PVL toxin released by MRSA (7). PVL provokes PMN necrosis or apoptosis (leukopenia). The injured PMN cells release chemokines, cytokines, and enzymes that in turn recruit further leukocytes and destroy epithelial cells, leading to inflammation (8) and necrosis (hemoptysis).

interval.[10] In this patient, we combined linezolid with rifampin, a combination that protects against rifampin resistance in methicillin-sensitive *S aureus* infections.[11] Rifampin has an "unlikely risk of teratogenesis."[8] Linezolid induced no toxicity or teratogenesis in our patient. Studies in rats and mice produced no evidence of teratogenicity at doses 4-fold and 1-fold the expected human exposure, despite mild toxicity.[12]

As our case report underlines, the clinical presentation may be misinterpreted and, if appropriate therapy is delayed, the infection rapidly progresses to severe pneumonia. Our patient manifested several characteristics described in other reported cases. For example, as in our case, and in most reported cases, CA-MRSA pneumonia affects young, healthy individuals.[13,14]

Our patient's disease had a subacute onset, with symptoms of an influenza-like syndrome, which is repeatedly reported in the literature to precede staphylococcal pneumonia.[3] *S aureus* has tropism for injured airway epithelium.

The infection also had a typical disease course, rapidly progressing within days to necrotizing pneumonia, followed by frank hemoptysis and leukopenia. Gillet et al.[3] reported a higher incidence of hemoptysis in patients with PVL-positive pneumonia than in those with PVL-negative pneumonia. Our patient's WBCs showed severe leukopenia, a frequent finding in cases of CA PVL-positive staphylococcal pneumonia.[13]

The pathogenesis of leukopenia, hemoptysis, necrotizing pneumonia, and the microorganism's high virulence are probably related to the toxins' mechanism of action. CA-MRSA produces β-channel pore-forming toxins, including PVL and α-hemolysin,[15] and other cytolytic peptides,[16] which create lytic pores in neutrophil and monocyte cell membranes, leading to leukopenia. Neutrophils release enzymes, chemotactic factors, and oxygen metabolites that produce severe inflammatory lesions (Fig. 2).[17] Whether the main virulence factor is PVL, α-hemolysin, or other peptides remains undefined.[15–17]

In our patient, a 4-week course of linezolid plus rifampin started at 14 weeks of pregnancy had a successful outcome without inducing toxicity or teratogenesis in the fetus.

REFERENCES

1. Kung HC, Hoyert DL, Xu J, Murphy SL. Deaths: final data for 2005. Natl Vital Stat Rep 2008;56:1–120
2. Vandenesch F, Naimi T, Enright MC, Lina G, Nimmo GR, Heffernan H, Liassine N, Bes M, Greenland T, Reverdy ME, Etienne J. Community-acquired methicillin-resistant *Staphylococcus aureus* carrying Panton-Valentine leukocidin genes: worldwide emergence. Emerg Infect Dis 2003;9:978–84
3. Gillet Y, Etienne J, Lina G, Vandenesch F. Association of necrotizing pneumonia with panton-valentine leukocidin-producing *Staphylococcus aureus*, regardless of methicillin resistance. Clin Infect Dis 2008;47:985–6
4. Broadfield E, Doshi N, Alexander PD, Greaves M, Woodcock A. Cunning and community-acquired pneumonia. Lancet 2009; 373:270
5. Mandell LA, Wunderink RG, Anzueto A, Bartlett JG, Campbell GD, Dean NC, Dowell SF, File TM Jr, Musher DM, Niederman MS, Torres A, Whitney CG. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis 2007;44(suppl 2):S27–72
6. Dumitrescu O, Boisset S, Badiou C, Bes M, Benito Y, Reverdy ME, Vandenesch F, Etienne J, Lina G. Effect of antibiotics on *Staphylococcus aureus* producing Panton-Valentine leukocidin. Antimicrob Agents Chemother 2007;51:1515–9
7. Cruciani M, Gatti G, Lazzarini L, Furlan G, Broccali G, Malena M, Franchini C, Concia E. Penetration of vancomycin into human lung tissue. J Antimicrob Chemother 1996;38:865–9
8. Friedman JM, Polifka JE. Teratogenic Effects of Drugs: A Resource for Clinicians (TERIS). Baltimore, MD: Johns Hopkins University Press, 2000
9. Bernardo K, Pakulat N, Fleer S, Schnaith A, Utermohlen O, Krut O, Muller S, Kronke M. Subinhibitory concentrations of linezolid reduce *Staphylococcus aureus* virulence factor expression. Antimicrob Agents Chemother 2004;48:546–55
10. Conte JE Jr, Golden JA, Kipps J, Zurlinden E. Intrapulmonary pharmacokinetics of linezolid. Antimicrob Agents Chemother 2002;46:1475–80
11. Murillo O, Domenech A, Euba G, Verdaguer R, Tubau F, Cabo J, Cabellos C, Gudiol F, Ariza J. Efficacy of linezolid alone and in combination with rifampin in staphylococcal experimental foreign-body infection. J Infect 2008;57:229–35
12. Product information. Zyvoxid, 2001
13. Francis JS, Doherty MC, Lopatin U, Johnston CP, Sinha G, Ross T, Cai M, Hansel NN, Perl T, Ticehurst JR, Carroll K, Thomas DL, Nuermberger E, Bartlett JG. 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
14. Adem PV, Montgomery CP, Husain AN, Koogler TK, Arangelovich V, Humilier M, Boyle-Vavra S, Daum RS. *Staphylococcus aureus* sepsis and the Waterhouse-Friderichsen syndrome in children. N Engl J Med 2005;353:1245–51
15. Bubeck WJ, Bae T, Otto M, Deleo FR, Schneewind O. Poring over pores: alpha-hemolysin and Panton-Valentine leukocidin in *Staphylococcus aureus* pneumonia. Nat Med 2007;13:1405–6
16. Wang R, Braughton KR, Kretschmer D, Bach TH, Queck SY, Li M, Kennedy AD, Dorward DW, Klebanoff SJ, Peschel A, Deleo FR, Otto M. Identification of novel cytolytic peptides as key virulence determinants for community-associated MRSA. Nat Med 2007;13:1510–4
17. Labandeira-Rey M, Couzon F, Boisset S, Brown EL, Bes M, Benito Y, Barbu EM, Vazquez V, Hook M, Etienne J, Vandenesch F, Bowden MG. *Staphylococcus aureus* Panton-Valentine leukocidin causes necrotizing pneumonia. Science 2007;315:1130–3