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Methicillin-Resistant *Staphylococcus aureus* USA300 Clone as a Cause of Lemierre's Syndrome▽

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We describe a case of a young woman who had methicillin-resistant *Staphylococcus aureus* USA300 clone (MRSA-USA300)-associated Lemierre's syndrome and secondary necrotizing pneumonia and cerebral infarcts. We also review 11 cases of *S. aureus*-associated Lemierre's syndrome reported in the literature from 1965 to 2010. Recognition of *S. aureus* as an emergent cause of Lemierre's syndrome informs the initial empirical antibiotic choice for this life-threatening condition and may positively impact patient outcomes.

CASE REPORT

A 22-year-old previously healthy Caucasian woman presented with a 2-week history of right neck pain and low-grade fever and a 1-week history of sore throat and nonproductive cough. She underwent a limited evaluation at the emergency department of hospital A, which led to treatment of symptoms with analgesics and discharge to her home. After her neck pain and fevers progressed within a week, she underwent reevaluation and admission to hospital A. A chest X-ray revealed nodular infiltrates in both lungs. The treating physicians ordered the initiation of empirical treatment with ceftriaxone after obtaining anaerobic and aerobic blood cultures. Soon after, the patient developed confusion; a computed tomography (CT) scan of the brain showed cerebral infarcts. She also received supplemental oxygen therapy for respiratory hypoxemia and distress. She underwent transfer to Barnes-Jewish Hospital (BJH). Upon arrival at BJH, she complained of throat and neck pain, cough, and shortness of breath. Vital signs revealed tachypnea and tachycardia. She had difficulty speaking due to inspiratory stridor and was unable to open her mouth completely due to pain. A physical exam revealed bilateral periorbital and facial edema, bilateral anterior cervical tenderness, and coarse breath sounds bilaterally. She also appeared mildly confused. The rest of the physical exam was unremarkable. Laboratory analysis revealed leukocytosis, anemia, and thrombocytopenia (white blood cell count of 15,000 [15.0K]/mm^3 [reference range, 3.8K to 9.8K/mm^3], with 95% neutrophil predominance, hemoglobin level of 11.0 g/dl [reference, 12.1 to 15.1 g/dl], and platelet level of 72K/mm^3 [reference, 140K to 440K/mm^3]). Basic metabolic panel and liver function tests were unremarkable. The treating physician admitted the patient to the intensive care unit (ICU). The ICU team empirically started the patient on intravenous vancomycin, ceftriaxone, and clindamycin. Soon after admission to the ICU, the team intubated the patient and initiated mechanical ventilation due to respiratory distress. Arterial blood gas analysis postintubation revealed a pH of 7.5, partial CO_2 pressure (pCO_2) of 31 mm Hg, and partial oxygen pressure (pO_2) of 135 mm Hg. Serum monospot and rapid HIV tests had negative results. Cerebrospinal fluid analysis revealed 314 nucleated cells that had 65% neutrophils, 15% lymphocytes, and 6% monocytes, a glucose level of 59 mg/dl (60% of serum glucose), and a protein level of 46 mg/dl. Blood cultures from hospital A grew *Staphylococcus aureus* resistant to erythromycin and oxacillin and susceptible to clindamycin, doxycycline, linezolid, trimethoprim-sulfamethoxazole, and vancomycin. Blood and cerebrospinal fluid cultures from BJH also grew *S. aureus*, with identical drug susceptibility patterns. CT scans of the neck and chest revealed thrombi in the right and left internal jugular vein and multiple septic emboli in the lungs. Magnetic resonance imaging (MRI) of the head showed multiple cerebral infarcts. A transesophageal echocardiogram performed on the same day as vancomycin initiation did not show any valvular vegetations. The clinical scenario led to the diagnosis of septic thrombophlebitis of the bilateral internal jugular veins, or Lemierre's syndrome, with septic emboli to the lungs and brain, secondary to methicillin-resistant *S. aureus* (MRSA). The patient's blood cultures turned negative after 48 h of vancomycin and clindamycin therapy. Clindamycin was discontinued after 7 days. Her hospitalization was complicated by acute respiratory distress syndrome (ARDS) and necrotizing pneumonia with subsequent development of bilateral pneumothoraces and bronchopleural fistulae. Her respiratory status improved gradually over the course of 1 month, and ventilatory support was eventually discontinued. She completed a 6-week course of trough-level-adjusted intravenous vancomycin therapy. Molecular typing of the MRSA isolate from her blood (16) revealed

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TABLE 1. Cases of *Staphylococcus aureus* Lemierre's syndrome

Reference for case	Age of Patient	Bacterium	Internal jugular vein(s)	Complications	Interventions[a]	Outcome
Hoehn et al. (15)	7 mo	MRSA-USA300	Left	Septic pulmonary emboli, empyema, pneumothorax, hemorrhagic pericardial effusion	Enoxaparin, i.v. heparin	Recovered
Kadhiravan et al. (18)	16 yr	MRSA	Bilateral	Septic pulmonary emboli, cavitation, right-sided pleural effusion, hemoptysis	None	Recovered
Puymirat et al. (29)	22 yr	MSSA	Right	Multiple pulmonary nodules, cavitation, cavernous sinus thrombosis	s.c. heparin, excision of IJ and EJ	Recovered
Boga et al. (3)	22 yr	MRSA	Right	Multiple small nodular lung densities, right-sided pleural effusion	i.v. heparin	Recovered
Herek et al. (13)	33 yr	MRSA	Right	Multiple septic pulmonary emboli, necrotizing pneumonia	None	Recovered
Bilal et al. (2)	30 yr	MRSA	Right	Bilateral cavitary lung nodules, right pleural effusion, bilateral cavernous sinus thrombosis, cranial nerve palsies	i.v. heparin	Recovered
Ceylan et al. (5)	80 yr	MSSA	Right	Bilateral pulmonary nodular infiltrates, bibasal pleural effusion	None	Recovered
Fong and Watson (11)	7 mo	MRSA	Right	Septic pulmonary emboli, cervical abscess, mastoiditis	Drainage of abscess	Deceased
Bentley and Brennan (1)	8 yr	MRSA	Left	Multiple pulmonary nodules	Aspirin on discharge	Recovered
Shivashankar et al. (33)	32 yr	MSSA	Left	Bilateral pulmonary nodules, pulmonary abscesses, cavernous sinus thrombosis; bilateral cerebellar, left frontal, and brain stem infarcts	i.v. heparin, activated protein C, warfarin	Recovered
Lim et al. (23)	32 yr	MRSA	Left	Pulmonary infiltrates; bilateral infectious aneurysm of the internal carotid artery; bilateral cavernous sinus thrombosis	i.v. heparin, endoscopic sphenoidotomy, endovascular coiling	Recovered

[a] Interventions in addition to broad-spectrum antibiotics. i.v., intravenous; s.c., subcutaneous; IJ, internal jugular; EJ, external jugular.

that it contained staphylococcal chromosomal cassette *mec* type IV (SCC*mec*IV) and clustered to multilocus sequence type 8 (MLS type 8), consistent with MRSA-USA300.

Discussion. Here we describe a case of a young woman who had methicillin-resistant *Staphylococcus aureus* USA300 clone (MRSA-USA300)-associated Lemierre's syndrome and secondary necrotizing pneumonia and cerebral infarcts. Failure to initially recognize the illness resulted in a delay in appropriate antibiotic administration and likely increased morbidity. Awareness of the clinical presentation of Lemierre's syndrome (fever and neck pain preceded by tonsillopharyngitis) (7) and of its causative agents will lead to timely and appropriate antibiotic administration and better outcomes. *Fusobacterium necrophorum*, an anaerobic Gram-negative bacterium, causes two-thirds of cases of Lemierre's syndrome; other causative organisms include *Streptococcus viridans*, *Bacteroides clostridiiformis*, *Peptostreptococcus magnus*, *Fusobacterium naviforme*, and *Eikinella corrodens* (20). Clinicians typically use beta-lactams, clindamycin, and third-generation cephalosporins to treat infection with these organisms. Reports have not frequently described *S. aureus* as a cause of Lemierre's syndrome (7). Without awareness of MRSA as a causative agent, clinicians may delay appropriate antibiotic coverage.

A PubMed search (http://www.ncbi.nlm.nih.gov/sites/entrez?db=pubmed) from 1965 to the present for septic internal jugular vein thrombosis caused by *S. aureus*, excluding cases secondary to intravenous catheters, revealed a total of 11 cases reported in the literature (Table 1). All of these cases were published after 2002. The articles describe a higher frequency of unilateral internal jugular vein thrombosis than of bilateral involvement. For all cases, metastatic spread to the lungs is reported; few involved the central nervous system. One elderly patient died. Only a single case, a 7-month-old infant who presented with a retropharyngeal abscess and left internal jugular vein thrombosis, had the causative *S. aureus* strain conclusively typed as MRSA-USA300 (15). To the best of our knowledge, we describe the first reported case of Lemierre's syndrome in an adult secondary to *S. aureus* conclusively typed as MRSA-USA300.

MRSA-USA300 has emerged as a cause of skin and soft tissue infections, prosthetic joint infections, and necrotizing pneumonia over the last decade (14, 21, 22). The reasons for its emergence remain unclear, but they likely relate to virulence factors unique to its biology that enable it to spread from person to person in the community and cause severe invasive disease in susceptible hosts (26). Among MRSA isolates recovered from patients in the United States, USA300 and USA400 were initially found among patients with no known hospital contact and therefore referred to as community associated. However, MRSA-USA300 has since been described as a cause of nosocomial infections (32), indicating spread of the organism to include health care settings. MRSA-USA300 as determined by pulsed-field gel electrophoresis (PFGE) corresponds to *S. aureus* MLS type 8 as determined by housekeeping gene sequencing or repetitive sequence PCR profiling and contains SCC*mec*IV (25). This clone is more likely than other types of *S. aureus* to be susceptible to ciprofloxacin, clindamycin, gentamicin, and trimethoprim-sulfamethoxazole (28).

The *S. aureus* isolate identified in this case caused a severe and unusual clinical syndrome. Delay in the institution of appropriate antibiotic therapy and other unidentified contributing factors could have accounted for progression of the infection. The young woman did not have any obvious reasons for immunocompromise (she was young and previously healthy; an HIV test was negative), but she was obviously susceptible to severe *S. aureus* infection. Currently unidentified host risk factors, perhaps defects in innate or adaptive immunity, could have accounted for an increased susceptibility to infection.

Likewise, the microbe could have had unique virulence factors that rendered it especially pathogenic; however, we did not examine the isolate for other virulence factors since it would not establish cause and effect in this case. Identification of a certain virulence factor in this *S. aureus* isolate would not necessarily mean that it is responsible for the clinical syndrome. Larger epidemiological studies that examine putative host risk factors for *S. aureus* infection coupled with microbe studies are needed to establish such associations.

Appropriate management of Lemierre's syndrome requires timely and appropriate antibiotic therapy. For severe MRSA infections, treatment options include vancomycin (first line), daptomycin, linezolid, and telavancin. Vancomycin serum trough levels should remain between 15 and 20 μg/ml for the duration of therapy (30). Daptomycin should not be used for cases with pulmonary involvement because it binds to lung surfactant and is thereby sequestered (34). Linezolid should be avoided in patients who are taking adrenergic or serotonergic medications due to its monoamine oxidase inhibitor activity (35). Telavancin, a newly approved lipoglycopeptide, is a promising alternative, especially for MRSA with intermediate resistance to vancomycin; however, telavancin is associated with a slight increase in nephrotoxicity compared to vancomycin (31). Combination therapy for severe MRSA infections is not superior to monotherapy and has in fact been associated with more side effects (10). For example, the concomitant use of gentamicin increases nephrotoxicity but only minimally improves outcomes (8). Antimicrobials should be continued until clot resolution, which usually occurs after 4 to 6 weeks of therapy.

The use of anticoagulation among patients with Lemierre's syndrome remains controversial (4). Clinicians should weigh the risks and benefits of anticoagulation very carefully for each case. No high-quality controlled trials exist to show the benefit of anticoagulation. A few case reports support the use of anticoagulation for septic internal jugular vein thrombosis (9, 27). These authors hypothesize that anticoagulation prevents septic embolization to distant sites. Other studies report harm from anticoagulation (15, 19). Involvement of the cavernous sinus is generally regarded as an indication for anticoagulation (9, 17). One review found that the use of intravenous heparin, followed by 3 months of warfarin, reduced morbidity among survivors (12).

Internal jugular vein ligation or excision is another important consideration in the treatment of Lemierre's syndrome. Ligation was commonly performed in the preantibiotic age. It is now rarely used and should be performed only in patients who demonstrate recurrent episodes of embolization despite treatment with antibiotics (6, 24). There are no specific data in cases of bilateral internal jugular vein thrombosis to guide the use of surgical ligation.

In summary, MRSA-USA300 is emerging as a cause of Lemierre's syndrome in addition to typically recognized organisms, such as *F. necrophorum*. Awareness of MRSA-USA300 as a causative agent of Lemierre's syndrome will guide empirical antibiotic choice and may positively impact patient outcomes.

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