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METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS* SEPTIC INTERNAL JUGULAR THROMBOPHLEBITIS: UPDATES IN THE ETIOLOGY AND TREATMENT OF LEMIERRE'S SYNDROME

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☐ **Abstract—Background: Lemierre's syndrome is classically precipitated by oropharyngeal infections that progress to suppurative internal jugular vein thrombophlebitis via direct extension. Metastatic pneumonia from septic emboli is nearly universal and bacterial seeding frequently results in disseminated septic foci. *Fusobacterium necrophorum* is the most commonly reported etiologic agent, though *methicillin-resistant Staphylococcus aureus* (MRSA) is an emerging pathogen and a myriad of oropharyngeal flora must be covered until blood cultures return. Prompt identification is paramount to minimizing morbidity. Empiric treatment with antibiotics exhibiting predominantly anaerobic activity has been standard, but now may be insufficient, given an evolving microbial landscape. Anticoagulation continues to be debated. Case Report: We describe an uncommon presentation of Lemierre's syndrome in a diabetic patient secondary to MRSA, where the only identifiable source of entry was atraumatic post-auricular cellulitis. Why Should an Emergency Physician Be Aware of This? Given the evolving landscape of organisms implicated in septic internal jugular thrombophlebitis, empiric treatment should entail consideration of MRSA. Patients at an elevated risk include those who are undomiciled or incarcerated, injection drug users, human immunodeficiency virus–positive, and have recently been hospitalized or completed a course of antibiotics. The existing evidence evaluating empiric anticoagulation is low-powered and retrospective and would benefit from randomized controlled trials. Although it does not appear valuable for most, those with thrombus extension, persistent bacteremia, or central venous thrombosis may benefit.**

☐ **Keywords—septic thrombophlebitis; internal jugular; Lemierre's syndrome; MRSA; oropharyngeal infection**

INTRODUCTION

Septic internal jugular thrombophlebitis is a potentially devastating disease first reported by Andre Lemierre in 1936. Initially termed *human necrobacilliosis*, it is a systemic condition that usually evolves from direct spread of a pharyngeal infection to the great vessels of the neck, with development of suppurative thrombophlebitis and subsequent bacterial seeding to the rest of the body as the septic clot fragments (1). *Fusobacterium necrophorum* was the classically implicated organism, though a multitude of oral flora has also been identified. Prior to the antibiotic era, most patients died from this condition due to multisystem involvement. In the modern area, mortality rates have ranged from 2% to 10%. Although there was a multi-decade decrease in reported cases over the course of the 20th century, the frequency of reports has been increasing, along with a worrying transition in the specific organisms implicated over the last 2 decades (1,2).

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CASE REPORT

A 49-year-old female with uncontrolled non-insulin–dependent diabetes mellitus presented to our emergency department with 2 days of numerous complaints. She had a severe throbbing headache associated with photophobia and unilateral left-sided tinnitus. Her neck was stiff and painful and she noted a fever of 101°F at home. Deep inspiration triggered right subcostal chest pain, although she denied an overt cough. She was nauseous, anorexic, and more constipated than usual. She denied recent surgery, trauma, i.v. drug use, or recent hospitalizations.

Her physical examination was notable for an afebrile, hemodynamic stable but toxic-appearing middle-aged female. Initial vital signs were temperature 98.1°F, heart rate 109 beats/min, blood pressure 117/71 mm Hg, respiratory rate 18 breaths/min, and SpO_2 100%. She was awake and alert, but ill-appearing and had difficulty participating in the history and examination due to pain. She exhibited photophobia and nuchal rigidity. Her otolaryngologic examination indicated subtle left postauricular cellulitis and left-sided cervical lymphadenopathy. She had severe left-sided neck tenderness upon palpation and was unable to ranger her neck due to discomfort. There was no oropharyngeal erythema, edema, tonsillomegaly, or exudates. She had coarse breath sounds in both lung bases. Cardiac examination was notable for tachycardia and a systolic ejection murmur. She had exquisite right upper quadrant tenderness that worsened with inspiration. Neurologic examination was nonfocal.

Integrated electronic medical records from another local emergency department indicated that she had an encounter for similar symptoms the day before. During that visit, she was also afebrile but noted to have nuchal rigidity. She had a leukocytosis of 21,800 cells/mm^3. Lumbar puncture was unremarkable. Computed tomography (CT) of the abdomen/pelvis was notable for a developing infiltrate in the visualized portion of the right lower lobe. A chest x-ray study was not performed. She was started on azithromycin for community-acquired pneumonia and discharged home from the emergency department.

Laboratory evaluation in our emergency department was significant only for leukocytosis of 15,700 cells/mm^3 (reference 4,000–10,000 cells/mm^3) and elevated inflammatory markers: C-reactive protein 41.60 mg/dL (reference <0.5 mg/dL) and erythrocyte sedimentation rate 61 mm/h (reference 0–20 mm/h). The rest of her laboratory values, including basic metabolic panel and liver function tests, were unremarkable. Initial lactate was normal at 1.9 mmol/L (reference 0.5–2.0 mmol/L).

CT of her neck with i.v. contrast was obtained to further explore her neck discomfort in light of the negative lumbar puncture the previous day. It was notable for left periauricular inflammation with an ipsilateral filling defect in the internal jugular vein (IJV) at the angle of the mandible (Figure 1) consistent with a nonocclusive thrombus. CT of her lungs highlighted a large right-sided non-layering pleural effusion and multiple bilateral non-cavitating pulmonary nodules and septic infarcts. This constellation of symptoms, laboratory results, and imaging findings were consistent with Lemierre's syndrome—suppurative thrombophlebitis of the IJV with subsequent seeding of the lungs with bacterial emboli.

Due to her septicemia at presentation, she was empirically started on broad-spectrum antibiotics including vancomycin and piperacillin/tazobactam, as well as metronidazole for additional anaerobic coverage, given the jugular vein findings. While in the emergency department, she developed mild hypoxia on room air to 87%, subsequently requiring 3 L nasal cannula. Head and neck surgery was consulted and suggested primary medical management. The admitting medicine team initiated a heparin drip, which was transitioned to enoxaparin and eventually discontinued at the time of discharge (18 days after admission). Antibiotics were narrowed to vancomycin when her blood cultures returned positive for *methicillin-resistant Staphylococcus aureus* (MRSA). Unfortunately, her right pleural effusion developed into an empyema and required video-assisted thoracoscopic surgery.

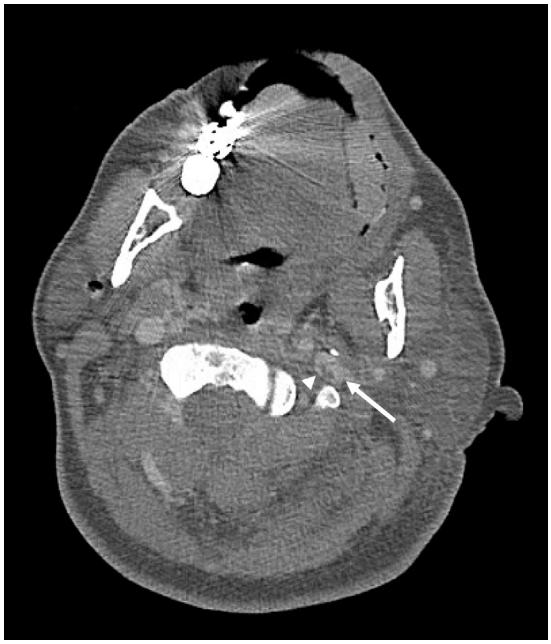

Figure 1. Contrast-enhanced soft-tissue computed tomography of the neck depicting the patient's partially occluded left internal jugular vein. Arrow: Left internal jugular vein. Arrowhead: Non-occlusive filling defect.

Table 1. Risk Factors for Methicillin-Resistant Staphylococcus aureus

Homelessness
Injection drug use
Incarceration
Human immunodeficiency virus
Recent hospitalization

Despite completing a 6-week course of parenteral vancomycin, she returned shortly thereafter with recurrent malaise and was found to have concomitant *Klebsiella* and *Enterobacter* bacteremia. It was presumed these new organisms were secondary to a line-associated infection, as she had become homeless during the outpatient treatment period and still had the indwelling catheter. On repeat CT imaging of her chest, her empyema and suppurative nodules had resolved; it is unclear if the jugular clot fully resolved, as her neck was not re-imaged. Anticoagulation was deferred. She proved unable to reliably visit the infusion center after her second discharge and was transitioned to oral ciprofloxacin. She was subsequently lost to follow-up.

DISCUSSION

Diagnosis of septic internal jugular thrombophlebitis is difficult due to a combination of low prevalence and a protean, time-variable presentation without pathognomonic features; this may unfortunately lead to erroneous diagnostic anchoring (1–3). Nuchal rigidity, as exhibited by our patient during her sentinel contact with the health care system, suggested meningitis. In other instances, scattered pulmonary nodules may allude to multifocal pneumonia or endocarditis.

History prototypically reveals a worsening oropharyngeal infection manifested as odynophagia, dental, or neck pain (1,2,4). As the disease progresses, patients may exhibit torticollis and nuchal rigidity as the carotid sheath and IJV become irritated through direct extension (5). Unstable clot forms as bacteria proliferate within the vascular lumen and invariably seed septic emboli to the central vasculature. Multifocal pneumonia (which may be complicated by parapneumonic effusions and empyema) is expected when the emboli become lodged in the pulmonary capillary bed (1,3). Metastatic septic involvement of nearly every organ system has been described, with central nervous system abscesses and stroke being the most devastating (1,2). Intracranial spread may present variably, depending on cortical, subcortical, or cerebellar distribution. Epidural abscesses may instigate back pain, focal numbness, or weakness, along with urinary retention or stool incontinence. Intra-abdominal involvement, typified by hepatic abscesses, can trigger right upper quadrant pain, nausea, and vomiting. Emboli to the musculature may lead to significant pain, particularly with movement of the affected muscle groups. Patients commonly appear toxic and a low threshold for intensive care unit admission is prudent, given the high risk of decompensation (1,4).

The classic etiology, *F. necrophorum* and related fusobacterial species, remain prevalent but *S. aureus* is an emerging isolate based on a temporal comparison of two recent meta-analysis by Karkos et al. in 2009 and Johannesen and Bodtger in 2016 (1,2). In the former study, which included 57 years worth of case reports in the antibiotic era, from 1950 to 2007, 86% (98 of 114 patients) grew *F. necrophorum* species and none were positive for *S. aureus* derivatives. Concerningly, in the 5-year period of case reports evaluated by the Johannesen and Bodtger from 2011 to 2015, only half of patients grew fusobacterial species (48 of 96) and they reported six *S. aureus* isolates, including two methicillin-resistant strains. There have been additional case reports of Lemierre's syndrome secondary to MRSA in the last few years since the latest meta-analyses (6,7). The significant rise of these case reports in the last few years is a curious finding. It is unclear whether this is due to a publication bias or if incidence is truly increasing (which has been posited as a consequence of evolving microbial resistance) (1,2,4). The evolving ecologic trend in bacterial isolates warrants re-assessment of empirical treatment guidelines.

Antibiotics remain the mainstay of treatment and have decreased mortality to <2%—only 2 of 137 patients died in the Johannesen and Bodtger review and neither death was attributable to fusobacterium (1). They must target oropharyngeal flora with coverage for emerging resistant organisms when appropriate. A non-pseudomonal β-lactamase–inhibiting penicillin (such as ampicillin-sulbactam) in addition to vancomycin, when the patient has risk factors for MRSA (Table 1), is appropriate (1,2,8). Local resistance patterns and the patient's antibiogram should always be considered. Inpatient treatment can be de-escalated based on culture results. Antibiotics are typically continued for 6 weeks due the presence of an infected clot and septic emboli to ensure complete bacterial eradication (9). If there are distant abscesses, early source control is imperative. Empyema in particular has thick rinds resistant to antibiotic impregnation and usually requires surgical drainage.

Contrasted CT of the neck vasculature is the cornerstone for identifying IJV thrombophlebitis, as it is readily available and accurate, diagnosing up to 95% of cases (1). Extending the CT acquisition through the thorax facilitates evaluating the scope of the pulmonary disease. Ultrasound is another diagnostic option in the emergency department and can quickly visualize a jugular vein

thrombus, but is less reliable and limited when the clot is cranial to the angle of the jaw (1).

Anticoagulation continues to be debated. Based on the most recent retrospective chart review by Cupit-Link et al., there were no differences in outcomes, but recommendations are limited, as evaluation rests solely on case reports and small overall sample size; randomized controlled trials are unavailable, even for septic thrombophlebitis in general (8). The currently advocated approach defers anticoagulation unless the patient remains persistently bacteremic (two positive blood cultures obtained on separate days of a specified illness), has a course complicated by central venous sinus thrombosis, or exhibits thrombus extension on repeat imaging (1,2,5,10).

WHY SHOULD AN EMERGENCY PHYSICIAN BE AWARE OF THIS?

Lemierre's syndrome is an uncommon cause of septicemia in the emergency department. It frequently masquerades as another disease process and a high level of suspicion is required to ensure appropriate diagnosis and to avoid diagnostic anchoring. Antibiosis targeting *F. necrophorum* and associated oral anaerobes is standard of care, but expanded treatment for MRSA should be considered. Patients at elevated risk include the undomiciled or incarcerated, injection drug users, human immunodeficiency virus–positive individuals, and those who have recently been hospitalized or completed a course of antimicrobials. The existing evidence evaluating empiric anticoagulation is retrospective and low-powered and would benefit from randomized controlled trials. Although it does not appear valuable for most, it may benefit those with thrombus extension, persistent bacteremia, or central venous thrombosis.

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