

# An Unusual Etiology of Lemierre-Like Syndrome: Preseptal Cellulitis due to Methicillin-Resistant *Staphylococcus aureus*

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Lemierre's syndrome (LS) is a rare and potentially fatal condition that predominantly affects young adults with oropharyngeal infection. *Fusobacterium necrophorum* is the usual etiology and classically causes internal jugular vein septic thrombophlebitis, frequently complicated by septic emboli to several organs (most classically to the lungs). Lemierre-like syndrome (LLS) describes the same constellation of symptoms and pathophysiology as Lemierre's syndrome; however, *Fusobacterium* spp. are not the cause, and the source of infection may be nonoropharyngeal. We present a case with an unusual etiology of LLS: a patient with untreated preseptal cellulitis and associated methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia in the setting of injection drug use. Physical exam revealed tachypnea and rhonchi with severe periorbital and bilateral eyelid edema. Imaging demonstrated bilateral preseptal and orbital cellulitis with thrombosis of both internal jugular veins and bilateral pulmonary cavitary lesions consistent with septic pulmonary emboli. She was managed with anticoagulation and parenteral antibiotics. To our knowledge, this is the first case of LLS originating from preseptal cellulitis without evidence of preceding pharyngitis. While facial and orbital infections are rare etiologies of LLS, the potentially devastating sequelae of LLS warrant its inclusion in differential diagnoses.

**Keywords.** injection drug use; Lemierre's syndrome; methicillin-resistant *Staphylococcus aureus*; preseptal cellulitis; septic pulmonary embolism.

Lemierre syndrome (LS) is characterized by internal jugular vein (IJV) thrombophlebitis and septic emboli in the setting of oropharyngeal infection due to *Fusobacterium* spp. [1, 2]. Lemierre-like syndrome (LLS) describes a similar pathophysiological process except in the setting of non-*Fusobacterium* or a nonoropharyngeal source of infection [3]. Both LS and LLS have a mortality rate of 2%–5% [2, 4]. Persons primarily affected are 15–24 years of age, with an annual incidence of about 14 cases per million [5, 6]. Treatment usually involves intravenous (IV) antibiotics in association with surgical drainage and debridement [5, 7, 8]. In only about 1% of cases have orbital infections been identified as triggers of LS and LLS [2]. In this case report, we describe a patient who developed LLS in the setting of untreated preseptal cellulitis with progression to orbital

and facial cellulitis due to methicillin-resistant *Staphylococcus aureus* (MRSA).

## CASE

A 33-year-old female with a medical history significant for injection drug use (IDU) and untreated chronic hepatitis C infection presented to an outside emergency department (ED) in October 2019 with 3 days of fever and a pruritic lesion adjacent to the right eye that became erythematous, warm, and tender. On presentation to the outside facility, she was febrile (39.4°C) with an exam remarkable for right-sided periorbital edema, which was tender to palpation. Her white blood cell count (WBC) was  $17.0 \times 10^6$  cells/L with 80.3% neutrophils on the differential count. Computed tomography (CT) of the head and neck with contrast demonstrated preseptal cellulitis without abscess. She was begun on therapy with IV vancomycin and IV ceftriaxone for empiric coverage. Unfortunately, the patient discharged herself shortly after admission to the outside facility, after which methicillin-resistant *Staphylococcus aureus* (MRSA) was isolated from her admission peripheral blood culture.

Two weeks later, she again presented to an outside facility with headache, facial pain, shortness of breath, and “pain everywhere,” after which she was transferred to our facility. Upon presentation, she was alert but oriented only to self with the following vital signs: blood pressure 137/79 mmHg, heart rate

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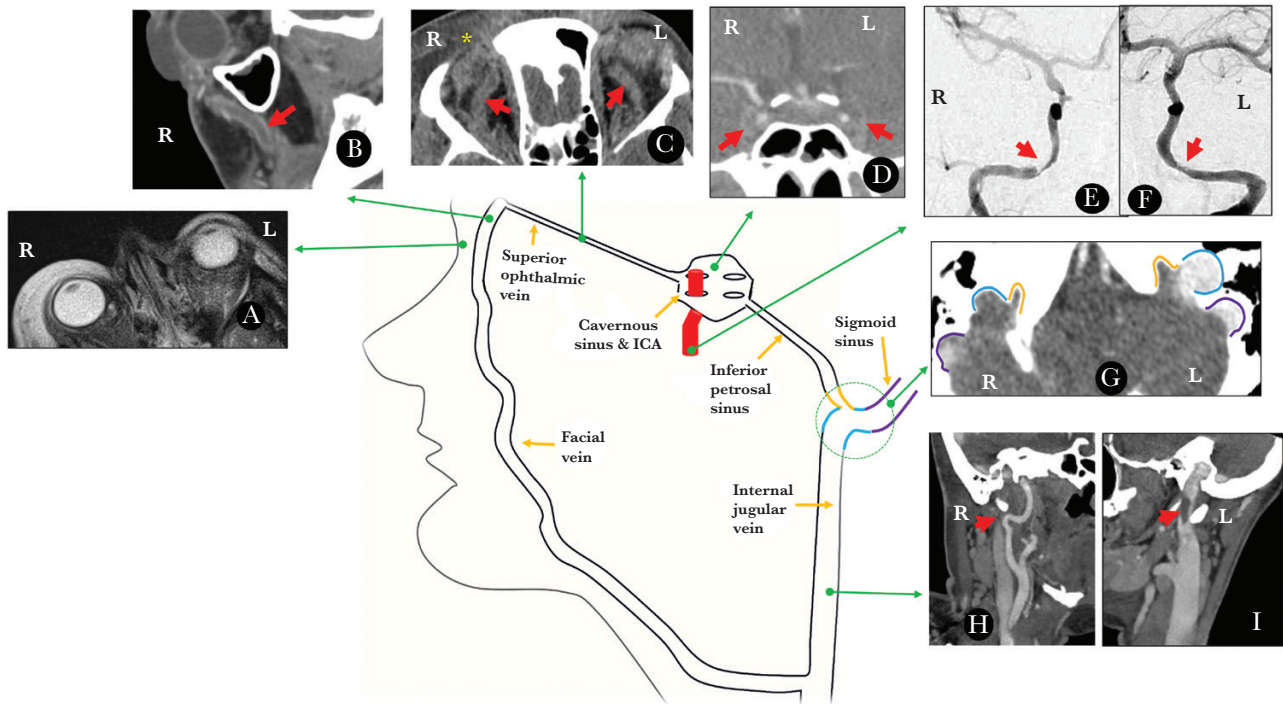
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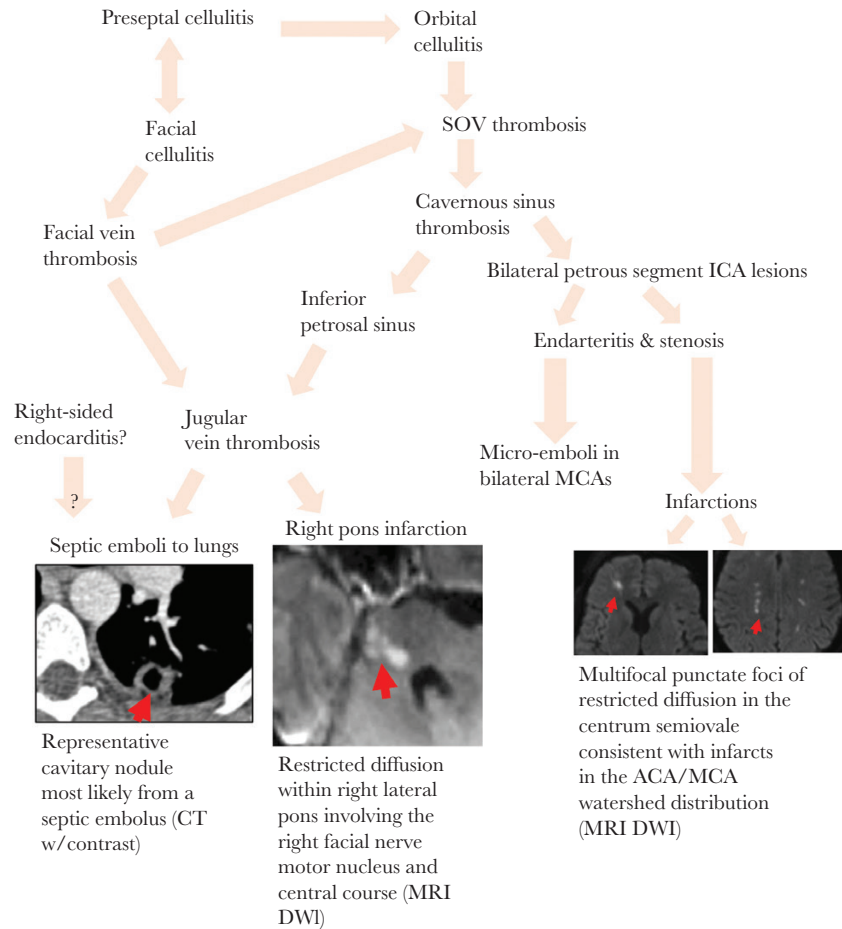
82 beats per minute, temperature 37.6°C, respiratory rate 26 breaths per minute, and oxygen saturation 97% on room air. She had bilateral severe eyelid edema and chemosis, right-sided peripheral facial droop without other focal neurological findings, and no nuchal rigidity. Cardiac findings were normal, but a pulmonary exam revealed diffuse rhonchi in all lung fields. Her laboratory studies were notable for WBC  $31.3 \times 10^6$  cells/L (91% neutrophils), C-reactive protein 409.9 mg/L, and erythrocyte sedimentation rate 97 mm/h. Peripheral blood cultures grew MRSA in both aerobic and anaerobic bottles. Minimum inhibitory concentrations (MICs) demonstrated resistance to oxacillin (MIC > 2 µg/mL) and susceptibility to clindamycin, erythromycin, gentamicin, vancomycin (MIC = 1 µg/mL), and daptomycin (MIC = 0.5 µg/mL). Her urine drug screen was positive for opiates and cocaine. A combination of CT of the head without contrast, CT perfusion, CT angiogram (CTA) of the head and neck, CT of the face with contrast, and magnetic resonance imaging (MRI) with and without contrast demonstrated bilateral facial, preseptal, and postseptal (orbital) cellulitis that was worse on the right side, with septic thrombophlebitis in multiple bilateral facial veins (Figure 1A–C). Thrombosis was noted in the bilateral cavernous sinuses, multiple dural sinuses, and bilateral IJVs (Figure 1D, G–I). Subsequent catheter cerebral arteriography demonstrated bilateral internal carotid artery

(ICA) stenosis likely secondary to endarteritis in the petrous sections (Figure 1E, F). MRI of the brain with and without contrast demonstrated infarcts involving the right lateral hemispheres and bilateral cerebral hemispheres in the watershed of the ACA/MCA vascular territories. A CT of the chest with contrast revealed innumerable solid nodules across all lobes with central cavitory components concerning for septic emboli (Figure 2). A transthoracic echocardiogram (TTE) did not demonstrate valvular vegetations.

The patient was admitted to the medical intensive care unit and begun on IV vancomycin for MRSA coverage. She was also anticoagulated with heparin for management of her extensive venous sinus thrombosis that involved her cavernous sinus. The patient's subsequent hospital course was highlighted by worsening of her ventriculitis and ACA/MCA watershed infarcts suspected to be secondary to stenosis of bilateral ICAs, which ultimately prompted neurosurgery to place a stent in her right ICA. A lumbar puncture was performed, and cerebrospinal fluid culture grew MRSA. Despite ongoing treatment with IV vancomycin, blood cultures continued to grow MRSA, so IV daptomycin was added empirically for attempted intensification therapy given the patient's progressive clinical deterioration and persistence of MRSA bacteremia. In light of her continuing signs of sepsis and her poor neurological prognosis,



**Figure 1.** Radiographic findings. A, Bilateral (R > L) preseptal and orbital cellulitis (MR T2 fat sat axial). B, Thrombosed right facial vein (red arrow; CT w/ contrast). C, Thrombosed bilateral superior ophthalmic veins and R > L preseptal cellulitis (yellow asterisk; CT w/ contrast). D, Bilateral cavernous sinus thrombosis (CT w/ contrast). E/F, Stenosis due to endarteritis of the petrous segments of both ICAs as highlighted by catheter arteriography. G, CT w/ contrast showing bilaterally thrombosed inferior petrosal sinuses (orange lines), right jugular bulb thrombosis (blue lines), and partially thrombosed right sigmoid sinus (purple lines). H/I, Right IJV with occlusive thrombosis superior to arrow (H) and left IJV with nonocclusive thrombosis (I) (CT w/ contrast). Abbreviations: CT, computed tomography; ICA, internal carotid artery; IJV, internal jugular vein; L, left; MR, magnetic resonance; R, right.



**Figure 2.** Proposed progression of disease in our patient. The infection started as a preseptal and facial cellulitis (right > left). This progressed to thrombophlebitis of the right facial vein, bilateral superior ophthalmic veins, bilateral cavernous sinuses, bilateral inferior petrosal veins, bilateral internal jugular veins, and right sigmoid sinus. The cavernous sinus thrombosis led to bilateral ICA stenosis and endarteritis (which resulted in bilateral MCA emboli and watershed infarctions). The patient also had bilateral pulmonary septic emboli, most likely from the thrombophlebitis in the IJVs, but right-sided endocarditis was not ruled out as a possible source of pulmonary lesions due to lack of TEE. The occlusive right IJV thrombosis also inhibited venous drainage from the right hemipons, leading to infarction in the right lateral pons involving the expected location of the facial nucleus and portions of the central course of cranial nerve VII; this explains our patient's presentation with peripheral right facial droop. Abbreviations: ACA, anterior cerebral artery; CT, computed tomography; DWI, diffusion-weighted imaging; ICA, internal carotid artery; IJV, internal jugular vein; MCA, middle cerebral artery; SOV, superior ophthalmic vein; TEE, transesophageal echocardiogram.

a goals-of-care discussion was held with her family, comfort care was initiated, and transfer to hospice was arranged. The patient died 3 weeks later.

## DISCUSSION

LS, a rare and a potentially fatal condition that predominately affects adolescents as a consequence of oropharyngeal infection, is associated with septic thrombophlebitis of the IJV with subsequent distal emboli. This syndrome was first described by Dr. André Lemierre in 1936. *Fusobacterium* spp. are the usual cause, and *F. necrophorum* (formerly *Bacillus funduliformis*) is the most commonly isolated organism [1, 2]. Only about one-third of invasive oropharyngeal *F. necrophorum* infections develop into LS [9]. The initial oropharyngeal infection is thought to damage the pharyngeal mucosa, facilitating spread of the

offending agent to the nearby peritonsillar vessels. Toxins released by *Fusobacteria* create a localized hypercoagulable state, leading to thrombosis of these veins. Thrombophlebitis of tributary veins results in spread of bacteria to the IJV, after which septic emboli are released into the systemic circulation, with the lungs being the primary downstream target [8]. Additional common complications include septic arthritis and osteomyelitis, central nervous system infection, and abscesses of various organs (eg, spleen, liver, lung) [2, 10]. LLS is the term used to describe a similar pathophysiology but accounts for variation in the anatomical source of infection (often nonoropharyngeal) as well as the causative organism (non-*Fusobacterium* spp.) [3].

Our patient's presentation is consistent with LLS—an orbital source of infection and MRSA as the causative agent. The suspected initial infection in our patient was MRSA-mediated preseptal cellulitis. Preseptal cellulitis refers to infection of the

soft tissues anterior to the orbital septum [11]. Similar to our patient's initial ED presentation, symptoms and signs are often limited to unilateral ocular pain, eyelid swelling, and erythema, but vision remains intact. In contrast, in postseptal (orbital) cellulitis, the infection occurs posterior to the orbital septum and is characterized by vision loss, pain with eye movement, ophthalmoplegia, and proptosis. Preseptal cellulitis can spread to become postseptal cellulitis. This progression likely occurred in our patient, particularly after she discharged herself from the first ED without sufficient antimicrobial therapy.

Her untreated infection presumably was accompanied by persistent bacteremia, as confirmed in the peripheral blood cultures at both the outside ED and in our ED. As has been reported in numerous other publications, persistent *S. aureus* bacteremia predisposes to development of metastatic foci of infection [12], which probably contributed to our patient's overall infectious burden and complicated clinical course. Subsequently, the infection likely tracked through small facial veins and superior orbital veins into the dural sinuses, ultimately leading to thrombosis of the IJVs (Figure 1H, I) and resultant septic pulmonary emboli (Figure 2). The burden of intracranial venous thrombosis led to venous infarction of the right lateral pons (explaining our patient's ipsilateral peripheral facial droop). Stenosis with suspected endarteritis of the bilateral ICAs resulted in multiple punctate infarctions in the anterior circulation as well as ACA/MCA watershed infarctions. ICA involvement has been reported in other LS and LLS cases [13, 14], and, while the pathophysiology is not explicitly clear, we suspect it is the result of contiguous spread of infection and inflammation in the IJV and cavernous sinuses. By the Duke criteria, our patient can be deemed to have had endocarditis (despite TTE not showing vegetations), and while right-sided endocarditis may have contributed to the septic pulmonary emboli, septic thrombophlebitis of the IJV is the more likely source. Unfortunately, our patient was not deemed stable enough to receive transesophageal echocardiography to better interrogate her cardiac valves.

The orbit is a very rare primary source of infection in LLS, as a recent literature review of 114 patients with LS and LLS found only 1 such instance [2]. A PubMed search using the terms (Lemierre\* AND orbit\*) yielded 6 case reports (Table 1) [15–20]. Only 2 of those reports described a primary orbital infection, although the case described by Kadiravan et al. may have been preceded by a primary oropharyngeal infection [19, 20].

Among Dr. Lemierre's initial cohort, mortality was 90% (18/20), with the treatment of choice being internal jugular vein ligation [1]. Fortunately, antibiotics have significantly decreased the incidence and mortality of LS and LLS [2, 21]. Generally, antibiotics should provide coverage for  $\beta$ -lactamase-producing strains of *F. necrophorum* as well as streptococci, with a duration of 3–6 weeks [4, 22]. While *F. necrophorum* is the most commonly isolated agent, recent studies have reported increasing

**Table 1. Orbital Infection or Sequelae in the Setting of Lemierre-Like Syndrome**

Age, y	Sex	Year of Study	Pathogen (Source)	Primary Infection	Orbital Complication	Antimicrobial Therapy (Duration if Specified)	Anticoagulation	Outcome
Aouad, Melkane, Rassi [15]	Male	2010	Methicillin-sensitive <i>Staphylococcus aureus</i> (blood, abscess)	Peritonsillar abscess	Right lid edema with multiple orbital abscesses	Broad-spectrum therapy	Yes (not specified)	Deceased
Akiyama et al. [16]	Male	2013	None	Facial cellulitis with tooth infection	Bilateral orbital cellulitis	Meropenem and clindamycin (6 wk)	Heparin	Recovered
Kahn et al. [17]	Male	2011	<i>Streptococcus milleri</i> (blood)	Likely pharyngeal infection	Bilateral orbital abscess	Vancomycin, meropenem, rifampin, penicillin, metronidazole	Heparin	Deceased
Olson et al. [18]	Female	2014	Group C <i>Streptococcus</i> (pharynx), EBV (serology)	Pharyngeal infection	Orbital abscess	Vancomycin, meropenem, clindamycin, trimethoprim-sulfamethoxazole	Enoxaparin, aspirin	Recovered
Camacho-Cruz et al. [19]	Female	2019	<i>Streptococcus anginosus</i> (orbit)	Postseptal cellulitis	-	Vancomycin (later replaced with linezolid for 14 d), ceftriaxone (21 d)	No	Recovered
Kadiravan et al. [20]	Female	2008	Methicillin-resistant <i>Staphylococcus aureus</i> (blood)	Likely pharyngeal infection	Postseptal cellulitis	In-hospital: vancomycin, metronidazole, cefoperazone-sulbactam Discharged: linezolid, metronidazole (4 wk)	No	Recovered

cases with MRSA as the implicated pathogen [3, 23]. Therefore, when risk factors for MRSA are present (ie, IDU, skin infection), vancomycin should be considered in early empiric treatment. In our case, untreated MRSA bacteremia, IDU, and preseptal cellulitis were all risk factors arguing for early vancomycin usage. As culture data become available, antibiotics can be adjusted accordingly and de-escalated as needed. Anticoagulation is a more controversial topic due to the absence of controlled studies. Although the majority of patients with LS and LLS are treated with anticoagulation [4, 21, 22], some providers only opt for anticoagulation if there is evidence of cavernous sinus thrombosis [24].

As our case exemplifies, a patient with untreated preseptal or orbital cellulitis has a risk of developing LS or LLS. Concurrent unusual or incongruent symptoms suggestive of metastatic complications distant to the face or orbit (ie, shortness of breath, arthritis, neurologic deficits) warrant including LS or LLS in the differential diagnosis. It is also important to keep LS and LLS in the differential (along with right-sided endocarditis) when encountering a patient with a history of IDU who is found to have septic pulmonary emboli. Appropriate imaging evaluation can confirm clinically suspected LS and LLS and evaluate for complications. Finally, our case underscores the growing body of literature showing MRSA as the cause of LLS in the setting of the opioid epidemic and the importance of providing empiric antimicrobial therapy for MRSA in a patient with a history of IDU or recurrent cutaneous abscesses suspected of having LS or LLS.

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**Patient consent.** Patient consent was unable to be obtained as the patient died before discharge. No identifying information is included in this case report. No human subjects experiments were conducted related to this case report; therefore, approval by local ethical committees was not indicated.

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