

Septic Pharyngitis and Thrombophlebitis in a Previously Healthy 16-Year-Old Boy

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Classic Lemierre syndrome is characterized by pharyngitis followed by septic internal jugular vein (IJV) thrombophlebitis, which is most frequently caused by infection with *Fusobacterium necrophorum*.¹ Although considered a rare disease today, Lemierre syndrome was relatively more common in the pre-antibiotic era, with 280 cases reported in the literature in 1955.^{2,3} The annual incidence was estimated at 1 case per million persons per year in the early 1990s.^{4,5} It is hypothesized that the common use of penicillin for throat infections led to the decline in cases of Lemierre syndrome.^{4,5} However, recent studies suggest that the incidence of the disease may be increasing.^{2,4,6,7} Potential reasons for the rising incidence include a downward trend in the use of antibiotics for sore throats or the development of *F. necrophorum* isolates resistant to penicillin and erythromycin.^{2,3,6} Alternatively, it is possible that more cases are being identified due to improvements in the ability to detect anaerobic bacteria.^{2,3,6}

This article describes the case of a teenage boy who presented with septic pharyngitis and thrombophlebitis. The systemic complications of Lemierre syndrome are discussed and the differential diagnosis and treatment of this clinical entity are reviewed.

CASE PRESENTATION

Initial Presentation and Evaluation

A previously healthy 16-year-old boy presented to the emergency department with a 1-week history of fever as high as 103°F (39.4°C). He complained of sore throat, headache, neck pain, and 4 to 6 hours of "locked jaw." He was unable to open his right eyelid fully. He had a 1-week history of decreased appetite and weight loss. Past medical history was significant for an episode of viral meningitis 2 years prior with normal recovery. The patient stated that he was sexually active and denied recent travel or ill contacts.

The patient was initially afebrile but later demonstrated fever and chills. He was interactive but appeared ill. Blood pressure was 103/80 mm Hg, heart

rate was 100 bpm, and respiratory rate was 20 breaths/min. Head, eye, ear, nose, and throat examination revealed right-sided ptosis; a right-sided, bulging, red, opaque tympanic membrane; trismus; and significant right-sided peritonsillar erythema and swelling. Neck pain was localized to the border of the right sternocleidomastoid, which was swollen and tender. There were petechiae on the patient's back. Physical examination of the heart, lungs, and abdomen was within normal limits.

Laboratory and Imaging Studies

Initial laboratory studies were notable for several abnormalities: white blood cell count, $22.3 \times 10^3/\mu\text{L}$ (normal, $4.5\text{--}13.0 \times 10^3/\mu\text{L}$) with 95% neutrophils (normal, 57%); platelet count, less than $10.0 \times 10^3/\mu\text{L}$ (normal, $150\text{--}350 \times 10^3/\mu\text{L}$); direct bilirubin, 4.1 mg/dL (normal, < 0.2 mg/dL); total bilirubin, 6.2 mg/dL (normal, 0.3–1.2 mg/dL); aspartate aminotransferase, 56 U/L (normal, 15–45 U/L); and C-reactive protein, greater than 20 mg/dL (normal, 0–0.7 mg/dL). An initial chest radiograph showed a possible early infiltrate. There was also an incidental finding of a right scapular osteochondroma.

Admission and Further Evaluation

The patient was admitted to the pediatric intensive care unit. On admission, the following studies were ordered: aerobic and anaerobic blood cultures; group A β -hemolytic streptococcus rapid antigen detection test and throat culture; urine culture; urine gonorrhea ligase chain reaction test; Epstein-Barr virus titers; HIV antibodies; and hepatitis A, B, and C serologies. The patient was given a platelet transfusion for thrombocytopenia. He

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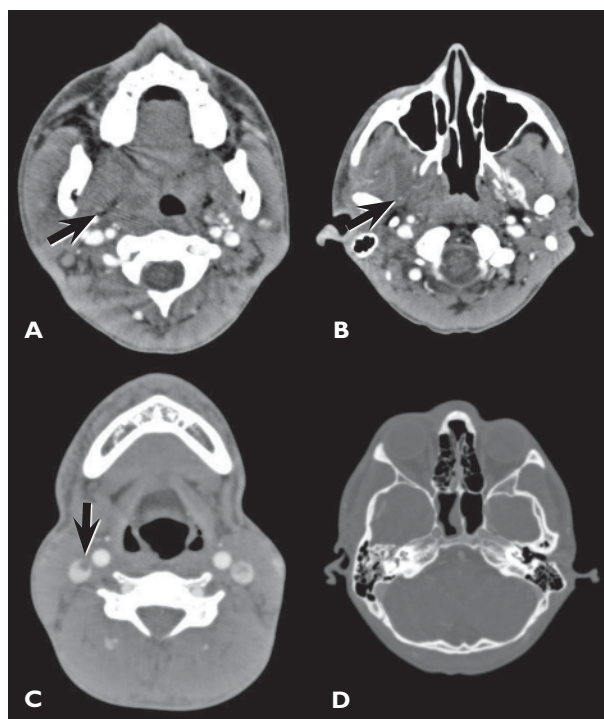


Figure 1. Axial contrast-enhanced computed tomography (CT) angiograms of the case patient's neck (soft tissue windows [A-C] and bone windows [D]) demonstrating (A) right-sided tonsillar abscess (black arrow) and swelling compatible with myositis of the masticator space muscles; (B) right-sided tonsillar thrombophlebitis (black arrow); (C) possible thrombosis of the right internal jugular vein (black arrow); and (D) opacification of the right middle ear cavity and mastoid air cells compatible with otomastoiditis.

was initially started on ceftriaxone 2 g intravenously (IV) every 12 hours and clindamycin 500 mg IV every 6 hours for presumed sepsis pending culture results.

Computed tomography (CT) angiogram of the neck showed right facial cellulitis and myositis; right-sided tonsillitis with multiple tiny abscesses and thrombophlebitis; opacification of the right mastoid air cells and middle ear; and possible thrombosis of the right IJV (Figure 1). CT angiogram also identified multiple pulmonary nodules in the lung apices suggestive of septic thromboembolic spread to the lungs (Figure 2). Color duplex ultrasound of the right IJV confirmed the presence of a partially occlusive thrombus (Figure 3). Based on the patient's clinical and radiographic findings, Lemierre syndrome was the suspected cause of the patient's symptoms.

Hospital Course and Treatment

The patient underwent a right tonsillectomy, incision and drainage of the right parapharyngeal abscess, and

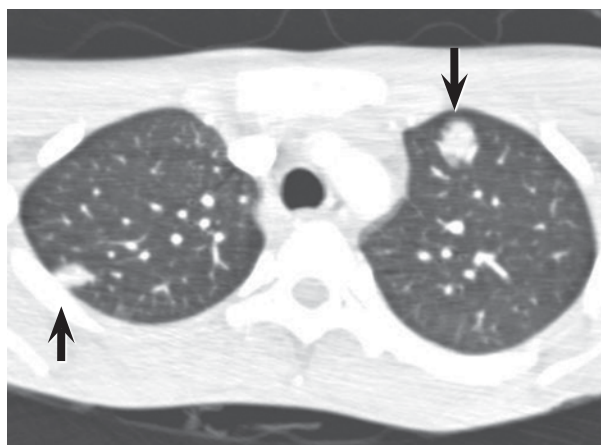


Figure 2. Contrast-enhanced computed tomography angiogram of the neck showing multiple pulmonary nodules (arrows).

right myringotomy tube placement on hospital day 1. He was started on enoxaparin for thrombosis prophylaxis. Late on hospital day 1, the initial anaerobic blood cultures were returned positive for gram-negative rods. At that time, ceftriaxone was changed to cefepime 2 g IV every 8 hours, and metronidazole 350 mg IV every 6 hours was initiated. By hospital day 3, the organism from the anaerobic blood culture was identified as *F. necrophorum*. At that point, antibiotics were narrowed to ceftriaxone 2 g IV every 12 hours and metronidazole 350 mg IV every 6 hours. The results of the remaining infectious studies were subsequently returned negative.

The patient developed left-sided pleuritic chest pain on hospital day 4. A CT scan of the chest revealed bilateral pleural effusions and pneumonia of the left lower lobe with superimposed atelectasis. Several small upper lobe inflammatory nodules possibly representing septic emboli were noted. By hospital day 7, follow-up chest radiography showed that the patient's pulmonary nodules became cavitory. A final chest radiograph taken on hospital day 29 showed complete resolution of the pulmonary lesions.

Jaundice, abdominal pain, and elevated liver enzymes developed within hours of admission, despite the normal appearance of the liver on right upper quadrant ultrasonography. These findings persisted for approximately 8 to 9 days and gradually resolved with no specific treatment aside from antibiotics for the infection. A mild pericardial effusion developed on hospital day 7 but resolved after 1 week with no specific intervention.

Follow-up imaging with magnetic resonance venography of the head and neck showed complete resolution of the right IJV thrombosis by hospital day 21, and enoxaparin was discontinued. However, a magnetic

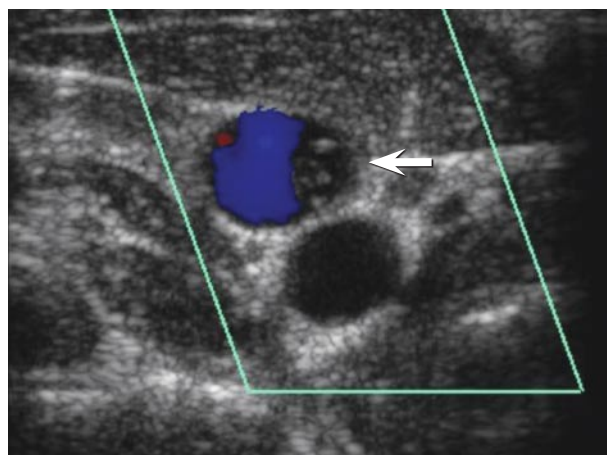


Figure 3. Color duplex ultrasound image of the neck demonstrating nonocclusive thrombus in the right internal jugular vein (arrow).

resonance image (MRI) of the head and neck taken on the same day showed right cavernous sinusitis and meningitis of the right middle cranial fossa, a focus of empyema along the tentorium, cerebritis, and a narrowing of the right internal carotid artery within the cavernous sinus (**Figure 4**). The patient was started on 81 mg of aspirin daily due to the right internal carotid artery narrowing. He was also switched from metronidazole to penicillin (due to nausea) at that time. A follow-up MRI taken on hospital day 28 showed resolution of the tentorium empyema, slow resolution of the otomastoiditis, persistent sphenoid sinusitis, and cerebritis. There was almost complete resolution of the neck inflammation and overall improvement in the degree of central nervous system (CNS) inflammation.

Because the patient's symptoms and laboratory abnormalities resolved, he was discharged on hospital day 30. He was instructed to continue aspirin 81 mg/day orally, ceftriaxone 2 g IV every 12 hours, and penicillin 4 million units IV every 6 hours for 4 more weeks. He recovered completely over the following weeks, with no neurologic or other sequelae. Follow-up MRI demonstrated significant improvement by 2 weeks and complete resolution of CNS inflammation by 2 months following discharge. Outpatient work-up revealed no underlying hypercoagulability or immunosuppressive disorders.

DISCUSSION

The differential diagnosis for the case patient's presenting symptoms was very broad. Infectious agents in the differential included group A streptococci due to the presence of pharyngitis; viral hepatitis due to the abnormal liver enzymes; Epstein-Barr virus due to both pharyngitis and abnormal liver enzymes; and HIV and

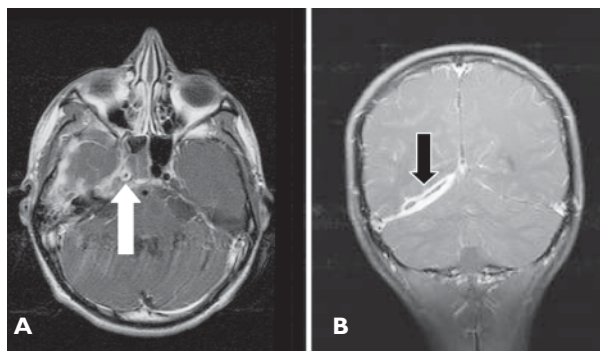


Figure 4. Contrast-enhanced magnetic resonance image of the case patient's brain. Both axial (**A**) and coronal (**B**) T1-weighted images demonstrate dural enhancement around the right temporal lobe. The right internal carotid artery is narrowed (white arrow), and there is an empyema along the tentorium (black arrow).

gonorrhoea due to the patient's sexual activity and diffuse symptoms. Leukemia and idiopathic thrombocytopenic purpura were considered due to the presence of thrombocytopenia. The initial chest radiograph was also suspicious for pneumonia. Ultimately, the combination of the patient's ill appearance, leukocytosis, thrombocytopenia, abnormal liver enzymes, and elevated C-reactive protein level led to a working diagnosis of sepsis. Lemierre syndrome was highly suspected based on the patient's pharyngitis and IJV thrombosis, and the diagnosis was confirmed by the blood culture, which was positive for *F. necrophorum*.

LEMIERRE SYNDROME

Clinical Presentation

The distinctive syndrome of postanginal sepsis with IJV septic thrombophlebitis was first described by Lemierre in 1936.¹ As seen in this case presentation, it is almost invariably associated with multiple systemic complications. Typically, patients with classic Lemierre syndrome are previously healthy adolescents and young adults who present with sore throat, fever, and persistent rigors. Patients also have painful lymphadenopathy and neck soft tissue swelling along the sternocleidomastoid muscle due to septic thrombophlebitis of the IJV. Within a week of symptom onset, patients develop metastatic abscesses from septic embolization to the lungs, pleura, bone, joints, skin, and soft tissues. Patients may rapidly progress to a fatal outcome if not diagnosed quickly and treated appropriately.¹

Pathophysiology

The organism most commonly associated with Lemierre syndrome is *F. necrophorum*.¹ Fusobacteria are gram-negative obligate anaerobic rods that are part

of the normal flora of the oral cavity, gastrointestinal tract, and female genital tract. *F. necrophorum* has an unusual ability to cause severe disease in previously healthy people, even with intact anatomic barriers.^{3,8,9} *F. necrophorum* possesses lipopolysaccharide endotoxin, which may account for the high fever and toxic presentation of infected individuals.^{2,3,5} *F. necrophorum* also produces lipase, leukocidin, and hemagglutinin, which may contribute to the unusually invasive nature of the infection and the ability to promote thrombosis.^{3,5} In vitro studies have shown that fusobacteria can aggregate platelets on contact without lysing them.^{2,3,6} Septic thrombi form in the tonsillar veins and then move centrally to involve the IJV. From the IJV, other metastatic emboli are spread throughout the body.^{2,5}

Diagnosis

Lemierre syndrome should be suspected in patients who present with pharyngitis and clinical signs of IJV thrombosis, such as tenderness and swelling along the sternocleidomastoid border. The presence of IJV thrombosis on ultrasonography and positive blood cultures for *Fusobacterium* confirm the diagnosis. Unfortunately, the diagnosis is often not suspected until blood cultures have returned positive for *Fusobacterium*, most likely due to a low index of suspicion among clinicians given the rarity of this disease. Also, the systemic nature of symptoms may distract clinicians from the original pharyngitis as a possible source.² However, with adequate knowledge of the syndrome, the diagnosis may be made quickly based on clinical presentation, which might afford earlier treatment and better outcomes.^{8,10} With prompt and appropriate treatment, the mortality rate from Lemierre syndrome can be reduced to less than 5%.^{2,5}

Complications

Metastatic emboli are responsible for the systemic complications associated with Lemierre syndrome. Between 80% and 100% of individuals with classic Lemierre syndrome develop pulmonary complications.^{2,3,8} Patients may initially complain of pleuritic chest pain and dyspnea. On chest radiography, lesions typically start as opacified nodules that frequently progress to cavitations. However, only rarely is there progression to acute respiratory distress syndrome or the need for mechanical ventilation assistance.^{2,11}

Other organs are less commonly involved. Gastrointestinal system involvement may include intra-abdominal and hepatic complications, which range from vague abdominal pain to frank jaundice in up to 49% of cases.^{4,11,12} Large bone and joint involvement ranging from arthralgias to septic arthritis can occur

in 15% to 30% of cases.² Renal manifestations are very rare, with acute renal failure occurring in less than 5% of cases.² Cardiac complications (eg, endocarditis, pericarditis) are rare.^{2,13} Although this case patient developed CNS complications, meningitis, cerebritis, and CNS abscesses occur in less than 4% of patients with classic Lemierre syndrome.² Septic thrombosis of cranial sinuses (including the cavernous sinus) is extremely rare and has been reported in only a handful of cases.¹⁴⁻¹⁸

Factors such as patient age and initial site of infection can predict the most likely associated complications. The classic presentation of pharyngitis, IJV thrombosis, and pulmonary involvement is commonly seen in the adolescent and young adult population. In children, *Fusobacterium* infections most often involve the middle ear, mastoid air space, sinuses, and/or peritonsillar regions but less commonly the IJV or the lungs. Therefore, children are more likely to develop meningitis. Immunocompromised individuals of any age but especially the elderly may be susceptible to a wide variety of infections not affecting the head and neck, including aspiration pneumonia, intra-abdominal infections, endometritis, and urinary tract infections. Initial infections caudal to the head and neck are less likely to develop IJV thrombosis commonly associated with classic Lemierre syndrome (Table).²⁻⁴

Treatment

Successful treatment depends on prompt administration of appropriate antibiotics along with surgical drainage of any initial abscesses. Several effective antibiotic combinations have been proposed in the literature.^{2,3,5,11-13} However, most regimens include the use of metronidazole or clindamycin in the empiric treatment of *F. necrophorum* infection until sensitivity results are available. Initial combination therapy is generally recommended due to the severity of the disease and the common presence of mixed infections. Prolonged antibiotic courses, ranging from 2 to 6 weeks, are often indicated.

Patients with Lemierre syndrome often remain febrile for up to several weeks despite proper antibiotic treatment. Prolonged fever may be caused by infection in poorly penetrable areas as well as by the presence of septic emboli, which contain bacteria that are protected from antibiotic activity by fibrin clots. Variable antibiotic resistance is also possible, especially with penicillins (2%–22%) and erythromycin (15%–22%);^{2,3,6} this resistance makes sensitivity testing of initial blood cultures vital.^{5,6}

Considerable controversy exists over the use of anticoagulants in Lemierre syndrome and the evaluation of patients for underlying thrombophilia. Due to the rarity of the syndrome, no prospective randomized trials

Table. Initial Site of *Fusobacterium* Infection and Associated Patient Factors/Complications

Site of Origin/ Initial Abscess	Age-Group	Previous Health of Patient	IJV Thrombosis/ Metastatic Lung Lesions	Meningitis
Peritonsillar (classic Lemierre syndrome)	16–19 yr	Invariably fit/healthy	More common	Rare
Ear and mastoid	Preschool children	Invariably fit/healthy	Rare	More common
Areas other than head/ neck	Varies	Immunocompromised/diabetes/ cancer/IV drug users	Rare	Rare

Data from Riordan T, Wilson M. Lemierre syndrome: more than a historical curiosa. *Postgrad Med J* 2004;80:328–34; Hagelskjaer Kristensen L, Prag J. Human necrobacillosis, with emphasis on Lemierre syndrome. *Clin Infect Dis* 2000;31:524–32; and Hagelskjaer LH, Prag J, Malczynski J, Kristensen JH. Incidence and clinical epidemiology of necrobacillosis, including Lemierre syndrome, in Denmark 1990–1995. *Eur J Clin Microbiol Infect Dis* 1998;17:561–5.

IJV = internal jugular vein; IV = intravenous.

have been performed. In addition, most patients recover from Lemierre syndrome without anticoagulation therapy.² However, most authors agree that any evidence of CNS thrombosis or cavernous sinus involvement, including cranial nerve palsy, warrants initiation of anticoagulant or antiplatelet therapy.^{2,3,14,19} Few reports comment on the need to evaluate patients with Lemierre syndrome for underlying thrombophilia because the pathogenic features of *F. necrophorum* explain the hyperthrombotic state seen in these patients. However, coexisting hereditary thrombophilia has been reported,²⁰ and some authors support evaluation for thrombophilia in patients with Lemierre syndrome.^{19,20}

CONCLUSION

In any previously healthy adolescent or young adult with septic manifestations, neck pain or swelling, and recent history of pharyngitis, Lemierre syndrome should be highly suspected. If the presentation includes pulmonary symptoms, abdominal pain, jaundice, and/or any thrombotic phenomena, early treatment using antibiotics with anaerobic coverage is indicated even before the results of blood culture are available. Anti-thrombotic drugs may also be considered. Awareness of the wide array of possible complications may help to guide therapy and monitoring as well as significantly reduce morbidity and mortality. **HP**

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