CLINICAL REVIEW

Lemierre's Syndrome – An Unusual and Dangerous Sore Throat

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Lemierre's syndrome is a rare and feared complication of pharyngitis characterized by septic thrombophlebitis of the internal jugular vein (IJV) and septic emboli (often pulmonary). LS typically begins as an oropharyngeal infection and usually effects otherwise healthy young adults. A link between prior Epstein-Barr virus infection (mononucleosis) and LS has been described. *Fusobacterium necrophorum* is the classical causative bacteria but other bacteria including *Streptococcus* and *Staphylococcus* have also been implicated. Diagnosis requires a high index of suspicion and is based on history, exam, blood cultures, and imaging tests showing IJV thrombosis. Diagnosis of this dangerous conditions is often delayed because many clinicians are unaware of this syndrome. Treatment includes antibiotics, drainage of local and metastatic abscesses, and consideration of anticoagulation. Primary care practitioners, emergency physicians and hospitalists, need to be aware of this "forgotten disease" as rapid recognition and treatment are paramount. We present a case of Lemierre's syndrome in a young woman following infectious mononucleosis and review the relevant literature on this disease.

Case Report

A 19-year-old female college student with no significant past medical history presented to the emergency room (ER) with sore throat, diffuse left neck pain and swelling, and fevers. She reported associated malaise, poor appetite, and odynophagia making eating difficult for several days. Two weeks prior, the patient developed a sore throat and was diagnosed at urgent care with infectious mononucleosis based on blood testing. She was prescribed a short course of oral steroids and acetaminophen/ hydrocodone as needed. Her symptoms had improved initially but over the past 4 days had recurred with worsening sore throat, new fevers, and severe diffuse left sided neck pain and swelling. She had been re-evaluated at urgent care and sent home with a diagnosis of suspected ongoing viral pharyngitis. She reported no other past medical history and denied drug use, sexual activity or a history of sexually transmitted illnesses, or any sick contacts.

In the ER, she was febrile with a temperature of 39.3°C, blood pressure 116/95 mmHg, heart rate 106 beats per minute, and oxygen saturation 98% on ambient air. She complained of left neck pain and appeared uncomfortable. Physical exam was significant for left neck swelling with tenderness to palpation from the jawline down to the base of the neck along the sternocleidomastoid muscle. Oropharyngeal exam showed left sided fullness. Her cardiovascular, pulmonary, abdominal, and skin exam was otherwise unremarkable. Initial laboratory testing showed an elevated white blood cell count (WBC) of 13.7 x 10^3/μL but was otherwise unremarkable. Ultrasound of the neck showed multiple "enlarged reactive lymph nodes" on the left neck. Chest radiograph was normal with no infiltrates, effusions, or masses. After obtaining blood cultures she was admitted to the hospital for close observation with initial suspicion for ongoing viral pharyngitis with reactive lymphadenopathy.

During the first night, the patient declined with worsening tachycardia, high fevers and ongoing neck swelling and a complicated infection was suspected. Ampicillin/sulbactam and vancomycin were started empirically and a computed tomography (CT) scan of the neck with intravenous contrast demonstrated phlegmonous changes of both tonsils with occlusive left jugular vein thrombophlebitis ("consistent with Lemierre's Syndrome") with significant adjacent inflammatory changes of the upper left neck. There was no dominant organized fluid collection. Also, a poorly characterized filling defect within the left sigmoid sinus which appears contiguous with jugular vein thrombosis was seen (**Figure 1** and **Figure 2**). CT venogram was recommended for further evaluation. Infectious disease, head and neck surgery, and hematology consultations were obtained and no urgent surgical intervention was recommended. Subsequent CT brain venogram showed thrombosis of the left sigmoid sinus and left internal jugular vein (**Figure 3**). Enoxaparin was started per hematology recommendations. Blood cultures from admission subsequently grew *Viridans group Streptococcus*.

Fever persisted for several days, but overall the patient slowly improved, and her WBC normalized. She was followed closely by head and neck surgery and did not require surgical intervention. Antibiotics were switched to ceftriaxone and metronidazole to complete two-weeks of intravenous treatment and she was subsequently given amoxicillin/clavulanate for an additional two-weeks (for a total of a four week course of antibiotic therapy). Enoxaparin was switched to apixaban upon discharge. The patient was diagnosed with suppurative thrombophlebitis due to *Viridans group Streptococcus* with bacteremia. These findings are consistent with 'Lemierre's syndrome' with the exception that no septic emboli to a distant site were identified. Two months after hospitalization, repeat CT brain venogram showed persistent thrombosis of the left internal jugular vein, jugular bulb and sigmoid sinus. She

followed up with hematology and continued apixaban treatment for 6 months. Her recovery was otherwise uneventful.

Discussion

In 1936, French bacteriologist Andre Lemierre described a group of young, previously healthy, adolescents or young adults who had a syndrome of initial pharyngeal infection followed by metastatic spread and neck swelling and tenderness along the sternocleidomastoid muscle due to internal jugular vein (IJV) septic thrombophlebitis. Subsequently, patients developed high fevers and rigors (sepsis) and metastatic abscesses from septic emboli. The disease was almost uniformly fatal with 18 of 20 patients dying.[1] The terms 'postanginal sepsis' and 'human necrobacillosis' are now used interchangeably with Lemierre's syndrome (LS). 'Postanginal sepsis' refers to the fact that septicemia often occurs after the resolution of the sore throat, while 'necrobacillosis' alludes to one of the causative organism's (*Fusobacterium necrophorum*) predilection to cause necrotic abscesses.[2] As described by Lemierre, infection starts in the throat and spreads locally by a septic thrombophlebitis to the ipsilateral IJV leading to bacteremia and septic emboli to other organs.[1,3] The causative bacteria, disease course, and treatment aspects are well described with timely recognition and appropriate antibiotic treatment being key to recovery.

LS is a rare disease (~ 1-3 case per million persons per year) that, for unknown reasons, characteristically occurs in otherwise healthy adolescents or young adults.[3] Recent literature suggest that the incidence of LS may be increasing due to decreased rates of tonsillectomy and decreased antibiotic prescription rates for pharyngitis as a result of antibiotic stewardship programs.[2-5] While LS classically has become synonymous with infection caused by *F. necrophorum*, an anaerobic Gram-negative bacilli, many other bacteria that are also normal oropharyngeal flora have also been implicated including streptococcus and staphylococcus species, enterococcus and others.[4-5]

LS classically arises from the oropharynx and leads to a complicated bloodstream infection. The exact route of infection is uncertain, but theories include hematogenous, lymphatic, or direct invasion through local tissues.[3] Primary infection is associated with pharyngitis in the tonsillar tissue followed by local invasion to the pharyngeal space causing septic thrombophlebitis of the IJV over 1-3 weeks.[3-5] While the exact pathogenesis is unknown, a common precipitating factor appears to be damage to the integrity of the oropharyngeal mucosal by bacterial or viral pharyngitis.[2] Case reports of LS occurring after "forceful oral sex" emphasize that mucosal disruption is key for bacterial translocation.[6] In addition, as was the case with the patient we present, multiple reports have described LS following Epstein-Barr virus (EBV) infection ('infectious mononucleosis').[7-9] It is suggested that EBV predisposes to bacterial infection by altering the mucosal barrier, causing lymphatic obstruction, and inducing immunosuppression through a transient decrease in T cell mediated immunity.[8-10]

Following invasion of the mucosal barrier, the proximity of the IJV allows further spread from the peritonsillar region into this vessel. Platelet aggregation and subsequent thrombus formation are a direct result of bacteremia and also serve as a source for septic emboli to other organs.[10]

Diagnosis is often delayed as many clinicians have not seen a case of LS and may not be aware of this condition. It is further complicated by the fact that metastatic complications often occur many days to several weeks after primary infection.[4-5] In his original description, Lemierre observed fevers and rigors as well as pulmonary infarcts and arthritic manifestations several days after onset of sore-throat.[1] Currently, in characteristic cases, young (age 16-30 years old) and otherwise healthy patients develop sepsis and appear acutely ill with high fever 4-5 days after onset of a sore throat. Eliciting a thorough history is key as in some cases the 'postanginal' interval between sore throat and septicemia can be prolonged (up to 1-2 weeks) and the sore throat may have subsided by the time of presentation. Once IJV thrombosis has occurred, patients often complain of neck pain or stiffness and cervical lymphadenopathy may be present. On exam, as was noted in the patient above, there may be tender swelling from the angle of the jaw extending down the sternocleidomastoid muscle which signifies IJV thrombophlebitis.[2,4,10]

Once thrombophlebitis has occurred, metastatic infection from septic emboli can mask the initial oropharyngeal symptoms. Septic emboli are most commonly seen in the lungs but can be seen in a variety of other organs as well (**Table 1**).[4,5] Pulmonary involvement is common (>80% of patients) and may result in pleural effusion, empyema, or abscesses. Chest radiograph typically shows nodular infiltrates or small effusions. Cavitary lesions, empyema (up to 15% of patients), and rarely even adult respiratory distress syndrome may develop. Septic arthritis occurs in around 20% of cases with the hip joint being most commonly affected. Osteomyelitis is less common (~3% of patients). Soft tissue lesions including muscle and abdominal wall abscesses can occur. Abnormal liver function tests (LFTs) are common and liver and splenic abscess have been described. Central nervous system (CNS) infections are rare.[2,10]

Classical cases of LS are defined by the combination of septic IJV thrombophlebitis, septic emboli, and sterile site infection by the classic bacteria *F. necrophorum* (most frequently blood cultures).[3] A high index of suspicion is key as patients can present with varied symptoms that mimic other common diseases. Frequently, patients have multiple visits to healthcare and are sent home with the diagnosis of a self-limiting viral illness. Despite the characteristic syndrome, the diagnosis of LS is frequently missed until blood cultures show an anaerobic Gram-negative rod or unexpected imaging findings of septic emboli.[3,10] Multiple case reports describe a similar presentation as the patient we report, where the clinical diagnosis was viral pharyngitis from infectious mononucleosis even at hospital admission.[2]

After a thorough history of recent illness and physical examination, blood cultures and neck imaging are key to definitive diagnosis of LS. Standard criteria for definite diagnosis of LS include a recent pharyngeal illness with subsequent septicemia (positive blood culture with *F. necrophorum* or other causative bacteria (*Streptococcus* or *Staphylococcus*), findings of septic emboli in one or more distant site, as well as findings of IJV thrombophlebitis.[4] On laboratory testing, patients typically have a neutrophil predominant leukocytosis, LFTs are elevated in about half of patients, and C-reactive protein is often very high. The key to the diagnosis of LS are culture data, with blood cultures being the most important.[2] As LS is often misdiagnosed as mononucleosis, it has been suggested that a unilateral neck swelling seen with IJV thrombosis together with a markedly elevated C-reactive protein can help distinguish these conditions.[8] As a result of infection reaching the IJV, hematogenous spread to other sites can occur leading to variety of additional complications and ultimately death if diagnosis and treatment are delayed (**Table 1**). Since pulmonary involvement is very common and may be present at the time of evaluation, LS can be misdiagnosed as acute pneumonia or right sided endocarditis.[2]

Imaging techniques are required to confirm IJV thrombophlebitis. Ultrasonography (US) is often the initial modality used as it is less expensive and avoids radiation exposure. However, US is less sensitive and is not adequate for imaging below the mandible, under the clavicle, and can miss newly formed thrombus with low echogenicity.[7] CT scan of the neck has higher sensitivity and is the preferred diagnostic modality.[2,4] If US is negative and suspicion remains, CT scan should be performed. In the case we report, US showed "reactive lymph nodes", and it was not until a CT scan was obtained that IJV septic thrombophlebitis was discovered. Magnetic resonance imaging (MRI) has excellent sensitivity as well but is much more expensive and less readily available. Both CT and MRI can identify thrombus and distinguish between IJV thrombosis and abscesses which can assist further management.[5]

There are no randomized trials to guide management of LS and recommendations are based on historical practice and limited evidence from observational studies and case reports. Multidisciplinary involvement of head and neck surgery, infectious disease, hematology, and other specialists if complications from septic emboli are present is advised. The key aspects of treatment include promptly administering antibiotics targeting the causative bacteria, drainage of infection at the primary and any metastatic sites if needed, and consideration of anticoagulation for IJV thrombosis.[2-5]

As the major pathogen *F. necrophorum* may produce β-lactamase, empiric treatment should include either metronidazole or a β-lactamase-resistant β-lactam. In addition, as infections can be polymicrobial, other oropharyngeal flora including streptococci should be also be covered. *F. necrophorum* is intrinsically resistant to fluoroquinolones and aminoglycosides and resistance to macrolides is common. Metronidazole is widely considered the treatment of choice for *F. necrophroum* and some data suggest it may be associated with the most rapid response. Advantages of metronidazole include activity against all isolates of *F. necrophorum*, excellent tissue penetration and high oral bioavailability.[3] A commonly suggested regimen is the combination of metronidazole (500 mg intravenous (IV) every 8 hours) and ceftriaxone (2 g IV every 24 hours) for coverage of *F. necrophorum* and other oral flora including streptococci. Monotherapy with a carbapenem or β-lactamase-resistant β-lactam (piperacillin-tazobactam or ampicillin-sulbactam) is also reasonable.[2-5]

As with other endovascular infections or those with necrotic foci, despite appropriate antibiotic coverage, clinical response can be slow with studies showing that fever can often persist for ~10 days. There is no general rule for the duration of antibiotic therapy or recommendations for when antibiotics should be switched from IV to oral. Treatment should be individualized based on severity, response to treatment, and metastatic sites of infection. Usually, antibiotics are continued to complete a 3 to 6-week course with close clinical follow up. Antibiotics are often given IV for 2 weeks or until the patient improves substantially and then switched to oral regimen (ideally including metronidazole).[2-5]

The next element of treatment is drainage of abscesses if necessary. Abscesses can form locally in the neck and septic emboli may lead to abscess formation in a variety of other locations. Surgical debridement of necrotic tissue may also be required. Prior to the use of antibiotics, ligation and resection of the IJV was commonly done. Today, it is only rarely required in extreme cases of uncontrolled sepsis or ongoing septic emboli despite treatment with antibiotics.[4-5] The patient we present was followed closely by head and neck surgery but due to CT findings of no distinct abscess and clinical improvement with antibiotic therapy, surgical debridement was not advised.

While anticoagulation is the mainstay of treatment for deep vein thrombosis and pulmonary embolism, its use in septic thrombophlebitis is controversial and it cannot be recommended in most cases of LS. From the available data, it remains unproven whether or not anticoagulation has any effect on thrombosis outcomes.[11,12] Use and duration of anticoagulation is highly variable in LS and appears to depend on the care provider. In many studies, a low percentage (20-30%) of patients are treated with anticoagulation and yet all patients do well and have similar outcomes. In a review of 18 patients in which only 6 patients received anticoagulation, all patients had similar improvement in their thrombi by 3 months, regardless of anticoagulation status, and the authors concluded that anticoagulation did not affect thrombosis outcome.[11] Some authors advocate that anticoagulation be reserved as an ancillary treatment for patients with thrombus progression to the cavernous sinus or CNS or in patients who have a hypercoagulable state.[11-13] Despite no prospective studies and poor data on efficacy, some have noted that anticoagulation use

is more common in recent years.[3] Clearly, based on current data, aggressive and prompt antimicrobial therapy is by far the most important part of management. Based on the extent of thrombosis in our patient, the anticoagulation was recommended by hematology consultants. Also, of note, the thrombosis in our patient did not resolve upon follow up several month later despite complete clinical resolution of her infection.

The illness from LS can vary in severity. Prior to antibiotics, LS was almost always fatal with death occurring in 18 out of 20 patients that Lemierre originally reported.[1] However, with antibiotic therapy, recovery is the norm and mortality has dropped from 90% to less than 5%.[3] It should be noted, however, that delays in antibiotic initiation can affect outcome with more deaths being reported in patients whose antibiotic therapy was delayed compared with those whom were promptly treated.[2]

Some authors have argued that the incidence of LS has increased in recent years due to clinicians avoiding prescribing antibiotics for sore throat as a result of antibiotic stewardship programs. Awareness of this rare syndrome is key to avoiding delays in treatment when these patients present to general practitioners. Some have suggested that patients with pharyngitis who have high fever with rigors, tender cervical lymphadenopathy and severe sore throat that lasts > 3 days should be tested for mononucleosis and have a CRP level tested. If heterophile antibody testing for mononucleosis is negative, antibiotic therapy should be considered.[14]

In conclusion, LS is a rare and serious infection that characteristically affects otherwise healthy young adults. A high index of suspicion is necessary as this disease can mimic other illnesses and diagnosis is often delayed. Patients typically present with high fevers, unilateral neck pain and swelling and other signs of sepsis. Clues to the diagnosis in our patient were the history of initial improvement then worsening of symptoms, unilateral neck swelling and high fevers. Blood cultures showing *F. necrophorum* or other implicated bacteria as well as CT scan of the neck showing IJV thrombophlebitis are diagnostic. As in the case presented, ultrasound can miss the diagnosis and CT is indicated if the diagnosis is unclear. Metastatic disease is common, with pulmonary involvement being by far the most common. Empiric antibiotic therapy that covers the most common organisms is essential and duration of treatment is typically 3-6 weeks. Drainage of purulent fluid collections may be necessary. Based on current evidence, anticoagulation is typically not necessary but should be carefully considered depending on the individual circumstances. With prompt diagnosis and antibiotics, LS is a curable disease and complications can be minimized.

Figures

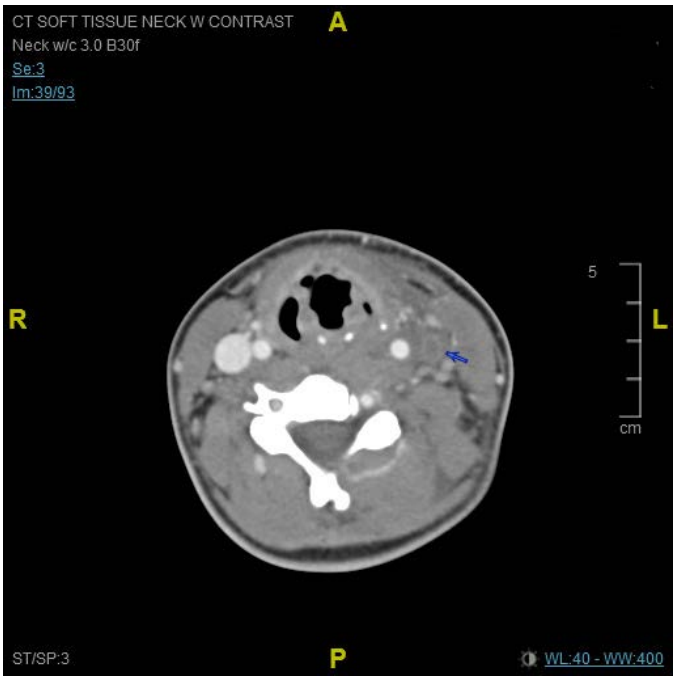

Figure 1. CT Scan neck with contrast (axial). Distended left jugular vein with centrally hypodense filling defect extending throughout the entirety of the jugular vein (arrow). Scattered enlarged bilateral cervical chain nodes, greater on the left – which are most likely reactive.

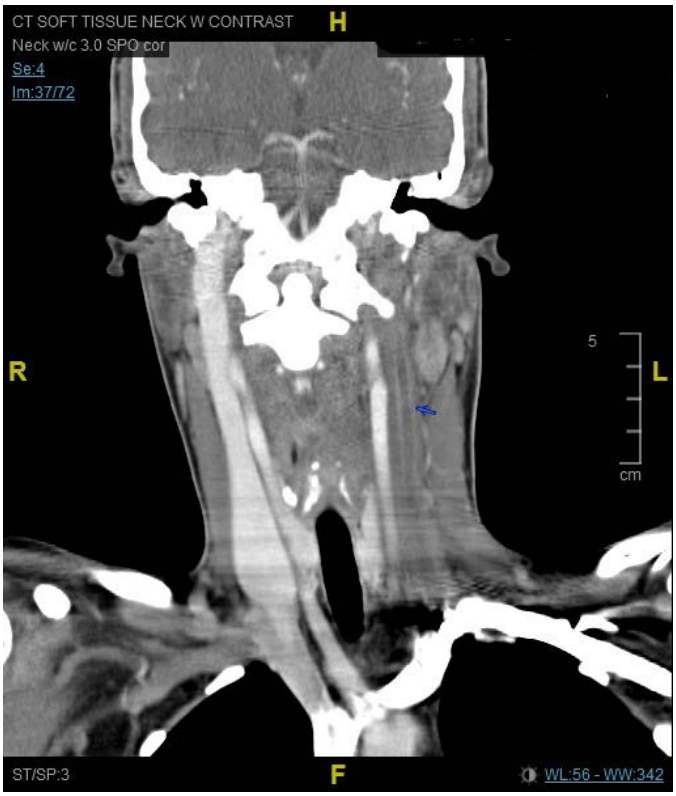

Figure 2. CT scan neck with contrast (coronal). Distended left jugular vein with centrally hypodense filling defect extending throughout the entirety of the jugular vein (arrow).

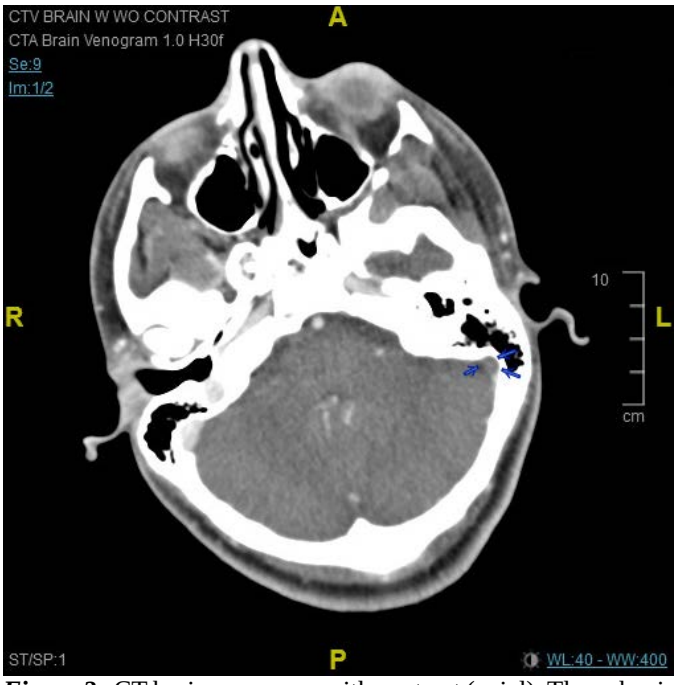

Figure 3. CT brain venogram with contrast (axial). Thrombosis of the left sigmoid sinus and left internal jugular vein (arrows). The thrombus ends at the left transverse sinus, which remains patent.

Table 1. **Potential Complications of Lemierre Syndrome***

A. Pulmonary (~80%) (septic emboli, infiltrates, abscesses, pleural effusion, empyema)
B. Septic arthritis (~20%) (large joints most common – hip, knee, shoulder)
C. Osteomyelitis (~3%)
D. Liver abscess
E. CNS (brain abscess, cavernous sinus thrombosis) - rare
F. Soft tissue abscesses

***** adapted from **Kuppalli K, Livorsi D, Talati NJ, Osborn M.** Lemierre's syndrome due to *Fusobacterium necrophorum*.. *Lancet Infect Dis.* 2012; 12:808-815.

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