

Lemierre's Syndrome presenting with neurological and pulmonary symptoms: Case report and review of the literature

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Abstract

Lemierre's Syndrome (LS) is a potentially life-threatening condition, characterized by clinical or radiologic evidence of internal jugular vein thrombosis following an oropharyngeal infection, most commonly by *Fusobacterium necrophorum*. A high index of suspicion and early recognition is important for successful management and to prevent systemic complications like multiorgan failure with extremely high morbidity, prolonged hospitalization and, not uncommonly, death. We are reporting a rare case of LS that was complicated with internal jugular vein and cavernous sinus thrombosis along with lung metastatic lesions, which was diagnosed and treated at our institute.

Key Words

Cavernous sinus thrombosis, lemierre's syndrome, pulmonary infiltrates

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Introduction

Lemierre Syndrome (LS), also known as human necrobacillosis, is a rare disease of the head and neck that often affects healthy adolescents and young adults, and is mostly caused by the anaerobic *Fusobacterium necrophorum*. Although initially described in 1900 by Courmont and Cade,^[1] it was the French microbiologist Dr. Andre Lemierre who best characterized the disease process in 1936.^[2] The disease is characterized by thrombophlebitis of the internal jugular vein and septic systemic embolism after a history of oropharyngeal infection. Infection originates in the oropharynx in the majority of the cases, but can also occur in the gastrointestinal and genitourinary tracts. Septic emboli are most frequent to the lungs, but can also involve the large joints and the kidneys.^[2] Since the term was coined in 1983, authors have generally limited use of the name "Lemierre Syndrome" to cases of oropharyngeal infection leading to thrombophlebitis in the

neck and associated septic emboli, although the name LS has been applied in a more expansive way for patients presenting with otogenic infection and even to disease process related to a central venous catheter.^[3-5] Thus, variable use of the term has prompted some authors to suggest more focused criteria for the syndrome, including clinical oropharyngeal infection, evidence of embolic disease, internal jugular vein thrombosis or isolation of *Fusobacterium* sp. from a normally sterile site.^[6]

Antibiotics along with anticoagulation therapy have lead to a markedly improved prognosis for patients with LS and a dramatic decrease in its incidence. The overall mortality has decreased since Lemierre's initial series from 90% to less than 6%.^[2,7] In view of the relatively low incidence of LS and its potentially confusing clinical manifestations, special emphasis is given to highly suggestive characteristic imaging findings on computed tomography (CT) imaging of the chest and the neck.

In an effort to emphasize the importance of early diagnosis and treatment of this once "forgotten disease," we present a report of the patient presenting with LS and also provide a comprehensive review of the current literature on its diagnosis and management.

Case Report

A 15-year-old previously healthy young female presented to the emergency department of our tertiary care institute with

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a 7-day history of high-grade fever, painful neck swelling, dry cough and progressive breathlessness. She also had history of vestibulitis of nose prior to onset of fever, but there was no history of chest pain, hemoptysis and orthopnea. On evaluation, she was febrile (100.4°F) with pulse-110/min, respiratory rate-30/min, blood pressure-100/60 mmHg and saturation at room air-86%. Her physical examination showed pallor, with taut and tender neck muscles. Small multiple tender cervical lymph nodes were also noticed. The oropharynx was normal and there was no evidence of parapharyngeal or retropharyngeal abscess on examination. Chest examination showed bilateral crepitation with reduced vesicular breath sounds on both bases. Central nervous system evaluation revealed left lateral rectus muscle palsy. Cardiovascular and gastrointestinal systems were unremarkable clinically. Her initial investigations showed a total leukocyte count of 16,400 cs/mm (neutrophils 85%, lymphocytes 15%), hemoglobin-8.5 gm% and platelet count-35,000 cs/mm, with normocytic normochromic blood film morphology. The clinical chemistry was unremarkable, except mild hypoalbuminemia. Chest X-ray showed evidence of right lower zone consolidation and pleural effusion [Figure 1]. In view of the above findings, an immediate possibility of neck vein thrombosis was considered and a contrast-enhanced CT and ultrasound Doppler of the neck were obtained, which showed left internal jugular venous thrombosis with multiple enlarged lymph nodes and subcutaneous edema [Figure 2]. A contrast-enhanced magnetic resonance imaging (MRI) of the brain was performed to localize the cause of left sixth nerve palsy, which revealed an area of nonenhancement in the left cavernous sinus suggestive of thrombosis [Figure 3]. A 2D-echocardiography was carried out to rule out infective endocarditis, which was also normal. Pleural fluid analysis showed neutrophilic predominant exudate with low glucose values and growth consisting of gram negative bacilli, identical in characteristics with *Fusobacterium*. She was initially being put on broad-spectrum i.v. antibiotics like augmentin and metrogl, which was changed in concordance with culture sensitivity results to meropenem, levofloxacin and teicoplanin. All other cultures including blood, sputum, urine and stool were sterile. Right empyema thoracis was drained but, in view of multiloculated collection, it also required intrapleural streptokinase instillation. The patient was continued on the above antibiotics along with oxygen supplementation and supportive treatment in the form of anticoagulants to which she responded dramatically and there was rapid improvement in the general condition of the patient. Anticoagulation was not given initially due to thrombocytopenia but, because the response to antibiotics was slow, anticoagulants were added in the form of low molecular weight heparin once her platelet count was above 75,000/mm³. She responded very well to the treatment and improved clinically as well as radiologically, with resolution of consolidation and effusion on serial chest X-rays. Anticoagulation was given for a total duration of 4 weeks and antibiotics were continued for a total of 6 weeks. Follow-up Doppler neck showed no evidence of residual internal jugular venous thrombosis. The patient has now recovered completely and is being followed-up in out-patient department on a regular basis for the last 6 months.

Discussion

Originally, LS has been described to be caused by the anaerobic, nonmotile, pleomorphic, gram negative bacillus

Fusobacterium necrophorum, commonly found in the oral cavity, gastrointestinal tract and the female genital tract. Current evidence suggests that this organism is responsible for 10% of

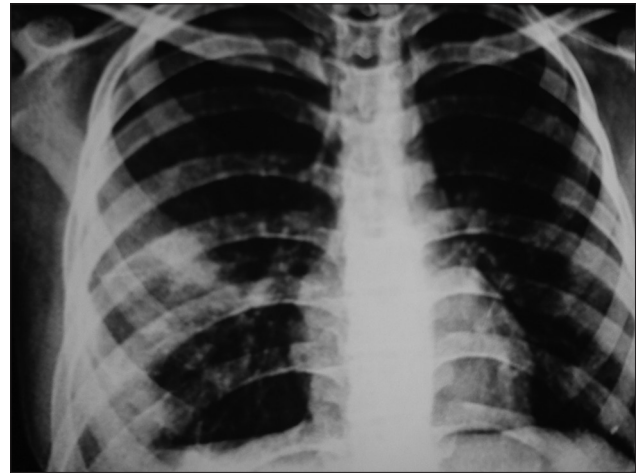


Figure 1: Chest X-ray showing pulmonary infiltrates on the right side

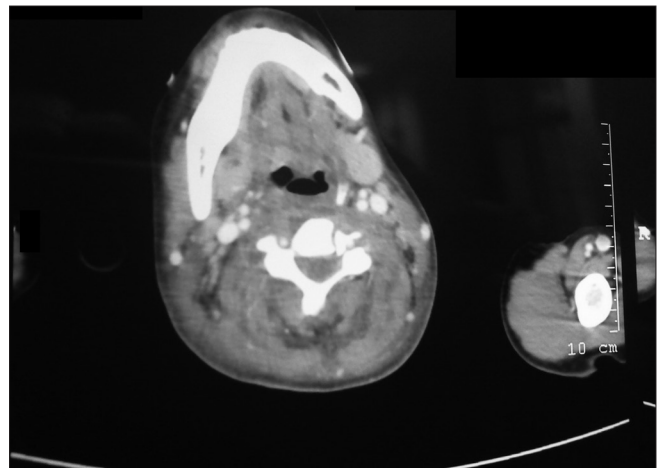


Figure 2: Contrast-enhanced computed tomography of the neck showing thrombosis in the left internal jugular vein (black arrow)

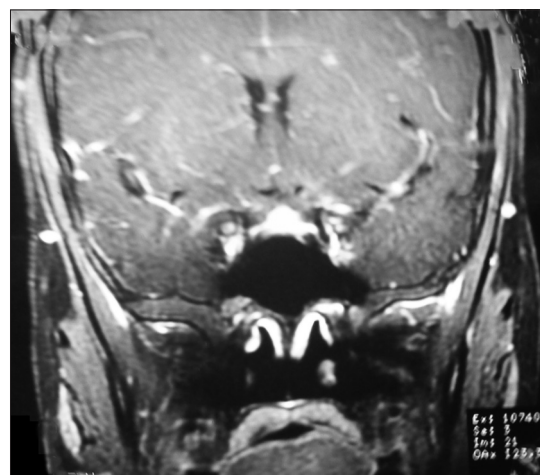


Figure 3: T1 image of magnetic resonance imaging of the brain showing nonenhancement in the left cavernous sinus indicative of thrombus formation

the new cases of pharyngitis and 20% of the recurrent cases.^[8] In the majority of the cases, *F. necrophorum* is the cause of LS, although a number of other anaerobic and aerobic organisms have been implicated, including Staphylococci, Streptococci, Proteus, Bacteroides and Peptostreptococcus.^[6] In the last 20 years, evidence suggests that the incidence of LS has increased.^[9,10] The reasons suggested for the reemergence of LS include macrolide antibiotic resistance, decreased rates of tonsillectomy, discouragement in the use of penicillin therapy for acute tonsillitis as well as improvement in diagnostic and blood culture methods.^[11] Although much is known about the progression of the disease, the ability of *F. necrophorum* to invade the mucosa is still unknown, and many believe that penetration of the bacterium is facilitated by weakening of the host mucosal defense system as supported by several reports of Lemierre's disease occurring in conjunction with Epstein-Barr virus pharyngitis and infectious mononucleosis.^[12,13] Furthermore, smoking has also been suggested as a factor contributing to *F. necrophorum* infection, as nicotine may enhance toxins from periodontopathogens.^[13]

Although the syndrome may affect patients of all ages, more than 70% of the cases have been documented in young adults between the ages of 16 and 25 years, similar to our case. LS is more common in males compared with females, contrary to our patient who was female.^[7,10] The pathogenesis proceeds through various stages, with disease beginning in the palatine tonsils and peritonsillar tissue in approximately 87% of the cases.^[7] Patients usually have a history of several days of febrile illness and sore throat in the first stage prior to the onset of more severe symptoms, although, in our patient, the disease process started with the vestibulitis of the nose.^[6,11] Clinical findings in the oropharynx may be deceptively mild, consisting of localized hyperemia or swelling, with little to suggest more extensive disease.^[10,11] Exudative tonsillitis, oropharyngeal ulcers, cervical lymphadenopathy and pharyngeal hyperemia are additional common findings at the onset of the disease.^[14] Tenderness developing along the lateral aspect of the sternocleidomastoid muscle represents the second stage of infection, with invasion of the lateral pharyngeal space leading to thrombophlebitis of the internal jugular vein and cervical lymphadenopathy, whereas invasion of the posterior compartment leading to cranial nerve X-XII palsies or Horner syndrome.^[7] Internal jugular vein thrombophlebitis often manifests as pain, dysphagia and unilateral swelling at the angle of the jaw, and is occasionally associated with trismus.^[15] In the final stages, spread of infection is observed with direct extension of the organism into the blood system or via septic emboli to the lungs or joints.^[6,7] The septic emboli in the lungs, the most common site of metastatic spread, can lead to empyema, lung abscess and pleural effusion.^[16] Pneumothorax and pneumatoceles have also been reported.^[6] Finally, frank respiratory failure requiring ventilatory support can also occur in about 15% of the cases, as described in one of the case series.^[7] Emboli to numerous other sites, including muscle, bone, brain and liver, have been described.^[6]

Little has been described about central nervous system involvement in LS in the literature. There are several descriptions of purulent meningitis caused by *F. necrophorum* in the classical LS, particularly in children, but is very rare.^[17]

A case of LS was described by Stokroos *et al.*^[18] with sigmoid sinus thrombosis, and he advocated the possibility of metastatic abscess in the brain or meninges from this foci. We consider that the cerebral infarction and subsequent brain abscess can be associated with the course of LS as cerebral infarctions, most of the time, develop at the same time despite different blood supply systems, and it can occur due to cerebral septic embolisms. However, as mentioned in the literature, venous thrombophlebitis usually does not lead directly to arterial infarctions and, hence, we suspect that the most likely cause is right-to-left cardiac shunt.

A sinister development of internal jugular venous thrombosis is retrograde propagation to involve the cranial sinuses, including the cavernous sinus or sigmoid sinus.^[19] Cavernous sinus thrombosis is a rare but often critical disease, which may not only be caused by infectious but also by noninfectious processes, including vascular, traumatic and neoplastic etiologies.^[20] Although septic cavernous sinus thrombosis is less common in the postantibiotic era, a delay in the diagnosis results in catastrophe.^[20] Nowadays, CT and MRI enable us to accurately diagnose cavernous sinus thrombosis by direct and indirect signs.^[21] In our patient also, we suspect that cavernous sinus thrombosis might have occurred through retrograde propagation of thrombophlebitis from the internal jugular vein, which led to left lateral rectus palsy and high-grade fever.

Septic cavernous sinus thrombosis has been reported to be accompanied by intracranial complications such as meningitis, brain abscess and subdural empyema, possibly as a result of spread from the same primary focus infection.^[20] It has been reported that cavernous sinus thrombosis is complicated by brain infarction.^[22] The cavernous portion of the internal carotid artery is occasionally narrowed or obstructed, which results in a diminished flow in the peripheral lesion.^[22] Spasm or inflammation of the arterial wall induced by arterial invasion of infection, or both, has been implicated for lesions in the intracavernous carotid artery.^[22] Recent reports showed that venous sinus thrombosis associated with septic cavernous sinus thrombosis is not restricted to the superior ophthalmic vein, and it is more common than previously thought.^[21] The veins and venous sinuses that communicate with the cavernous sinus are valveless and, therefore, thrombophlebitis may affect the cavernous sinus in a retrograde fashion. Cavernous sinuses drain the blood from the orbits and the anterior part of the base of the brain via the sphenoparietal sinus and the middle cerebral veins. As a result, thrombosis can extend from the cavernous sinus to the other dural venous sinuses. Thus, hemorrhagic infarction can develop due to thrombophlebitis of the tributaries of the cerebral venous sinuses. Hypopituitarism is a rare complication of cavernous sinus thrombosis, possibly related to infectious necrosis or aseptic infarction of the gland, which can develop more than 1 year after the initial event.^[20]

A high index of suspicion is the key to correct diagnosis. Diagnosis is primarily clinical because blood culture for *Fusobacterium* may require incubation for 6–8 days, although blood culture positive for *F. necrophorum* is usually the first diagnostic clue.^[7] In our case, diagnosis of LS was made in view of history and clinical examination, which was then confirmed with radiological investigations and culture of pleural fluid. All other routine cultures were negative in our case.

With suspected clinical picture, imaging modalities usually confirm the diagnosis. Chest radiographic findings are nonspecific and may include ill-defined nodules or masses, cavitary lesions and focal areas of airspace disease.^[14] Contrast-enhanced CT provides exceptional accuracy in the diagnosis of LS because of its ability to show distended neck veins with enhancement of the walls, low attenuation intramural filling defects and swelling of the adjacent soft tissues, which allows the delineation of additional pathology (e.g., abscess extension) and sensitive visualization of the intrathoracic veins. Also, in cases with pulmonary involvement, it gives a better delineation of the pathological findings of the lung.^[14,23] Ultrasonography has also been used to identify internal jugular vein thrombosis, showing an echogenic region within a dilated vein or a mass consisting of both solid and cystic components.^[16,24] The use of magnetic resonance angiography, gallium scans and radionuclide venography with Tc 99m-labeled RBCs has also been reported.^[23,24] Metastatic infection can be identified through multiple diagnostic modalities. Abdominal ultrasound can identify liver or splenic abscess.^[23,24] Aspiration and culturing of joint fluid are indicated when patients develop arthritis, as is culturing of skin pustules when skin infections are present.^[23,24]

The combination of early diagnosis with aggressive intravenous antibiotic treatment covering anaerobes needs to be started as soon as possible because LS is a potentially fatal condition with a mortality rate of about 4–18%, and a rapid start of treatment is important for a good clinical outcome.^[7,25] The use of anticoagulation therapy along with intravenous antibiotics remains controversial.^[9] Moore *et al.* state that in a review of 41 cases of LS, 11 patients were found to have improved following the addition of anticoagulation treatment thus endorsing its use in cases of extensive thrombosis.^[26] Golpe *et al.* reported that it may be useful if septic emboli persist despite antibiotic therapy or if thrombosis propagates to the cavernous sinus.^[13] The mechanism of clot formation, especially in the internal jugular veins, is secondary to an inflammatory and septic process. Patients are not generally at increased risk for coagulopathy after resolution of LS, but these patients have been shown to display increased factor VIII activity as well as antiphospholipid antibodies.^[27] Opponents of anticoagulation argue that the clots associated with LS generally resolve on their own and outcome is good for the patient, but proponents of anticoagulation support its use for quicker resolution of clots. We believe that hastening the resolution of septic emboli is of significant clinical importance, and our treatment protocol is to give anticoagulation therapy whenever patients of acute infection present with thrombosis and septic emboli.

Standard treatment for jugular thrombophlebitis and LS has still not been established, but high-dose penicillin, metronidazole, clindamycin and chloramphenicol are recommended as antibiotics. However, these drugs may require 3–6 weeks to exert an effect, although the duration of treatment can vary from 9 to 128 days, as reported in the literature.^[10,13,27] The response of the infection to treatment is usually slow because bacteria sequestered inside of a septic thrombus in the internal jugular vein or inside of a deep abscess in the lung or liver may not be accessible.^[10] Duong and Wenger recommend metronidazole and beta-lactam agents (amoxicillin–clavulanate, ticarcillin–clavulanate

and cephalosporins), taking into account that some *Fusobacterium* strains produce b-lactamase.^[28] According to Simon's antibiotic susceptibility tests, *F. necrophorum* was highly sensitive to ampicillin, chlortetracycline, cephalothin, chloromycetin, doxycycline, lincomycin, methacycline, penicillin, oxytetracycline and tetracycline, but all isolates of *Fusobacterium* tested were resistant to bacitracin, dihydrostreptomycin, kanamycin, naladixic acid, neomycin, streptomycin and sulfadiazine.^[29] Because our patient had an acute condition and also had septic emboli in the lungs, antithrombotic drugs were administered and the patient improved dramatically, which was confirmed by serial chest X-rays. More aggressive therapies including venous ligation and resection of thrombosed veins have also been employed, but this is generally reserved for patients with continued septic emboli.^[7,11] In general, the prognosis for full recovery is good in patients given prompt and appropriate therapy.^[7] LS was once called the "forgotten disease" because of its rarity, but it may not be that uncommon anymore.^[30]

Conclusion

Although a rare clinical entity today, LS is a disease of considerable morbidity and potential mortality. This case is being reported as very few studies are mentioned in the literature where LS presents with cavernous sinus thrombosis and occurs after vestibulitis of the nose. Timely recognition of disease progression is crucial in preventing severe systemic manifestations. To avoid diagnostic delays, we advocate the early use of CT/ultrasound imaging of the neck and the chest. Empirical broad-spectrum antibiotic treatment should not be delayed, and should always include a third-generation cephalosporin. Lastly, we recommend the use of anticoagulation in individuals with confirmed jugular thromboses to expedite recovery in such patients.

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