From a sore throat to Lemierre syndrome. A case report and literature review

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Abstract

A 17-year-old male patient presented to our emergency department for fever, persistent sore throat and right-sided neck pain despite antibiotics, and dehydration. He was found to have thrombosis of the right facial vein and diffuse septic emboli. Blood culture tested positive for *Fusobacterium necrophorum*, leading to a diagnosis of Lemierre Syndrome (LS). LS is a life-threatening condition characterized by thrombosis of the internal jugular vein, anaerobic bacteraemia, and diffuse septic emboli. It should be suspected in healthy young patients who present with persistent sore throat or atypical lateral cervical pain, followed by sepsis and bronchopneumonia. Diagnosis is confirmed through the identification of jugular venous thrombosis and is supported by the growth of anaerobic bacteria in blood cultures. Treatment is based on prolonged targeted antibiotic therapy and hydration. The indication for anticoagulant therapy remains a topic of debate. Our patient was treated with antibiotics and anticoagulant therapy, resulting in a good clinical response and subsequent complete recovery.

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Highlights

- *Lemierre Syndrome (LS) is a rare but potentially life-threatening septic condition;*
- *LS usually begins with pharyngotonsillitis primarily affecting young adults;*
- *LS manifests as thrombophlebitis of the internal jugular vein, diffuse septic emboli, and anaerobic septicaemia;*
- *Fusobacterium necrophorum is often identified as a causal agent;*
- *Early recognition and prolonged antibiotic therapy are essential to prevent mortality and severe permanent complications.*

Introduction

Lemierre Syndrome (LS) was first described in 1900 by Courmount and Cade, who reported a case of suppurative internal jugular vein thrombophlebitis associated with oropharyngeal infection.[1] In 1936, the French microbiologist André Lemierre described a series of 20 cases of "post-anginal septicaemia".[2,3] The syndrome is characterised by a recent oropharyngeal infection, thrombosis of the internal jugular vein, and severe anaerobic septicaemia generally caused by *Fusobacterium necrophorum*. Starting with the description of a case of LS in a young male patient, we conducted a review of recent data regarding the epidemiology, etiopathogenesis, clinical presentation, diagnostic criteria, and treatment of this syndrome. Our research involved a comprehensive review of the relevant literature available on PubMed and Google Scholar from 2015 to the present.

Case Report

A 17-year-old male patient, who had been in excellent health

until a few days prior, presented to our emergency department for high fever, asthenia, headache, and pharyngodynia persisting for the past two days and not responsive to azithromycin 500 mg daily and oral ketoprofen 80 mg q12h. He also reported right-sided neck pain and odynophagia. His medical history included retinoblastoma with the enucleation of the right eye in early childhood and a few episodes of pharyngotonsillitis. He denied any allergies. At admission, his vital parameters were as follows: blood pressure 90/60 mm Hg, heart rate was 123 bpm, and body temperature 35.8°C. Physical examination revealed pharyngeal hyperaemia with slight whitish exudate, as well as swelling of the submandibular lymph nodes. Cardiac, pulmonary, and abdominal evaluation was normal. Laboratory tests documented increased inflammation indexes with C-reactive protein 331 mg/dL (normal value <5) and procalcitonin 99.20 mcg/L (normal value <0.5) with leucocytosis (WBC 16,800/mm^3 - neutrophils 93%), and renal damage with creatinine 2.05 mg/dL (normal value 0.70-1.20) and normal serum electrolytes (Table 1). Epstein Barr serology, Legionella and pneumococcal urinary antigen resulted negative. Chest X-ray, electrocardiogram, and abdominal ultrasound bedside were normal.

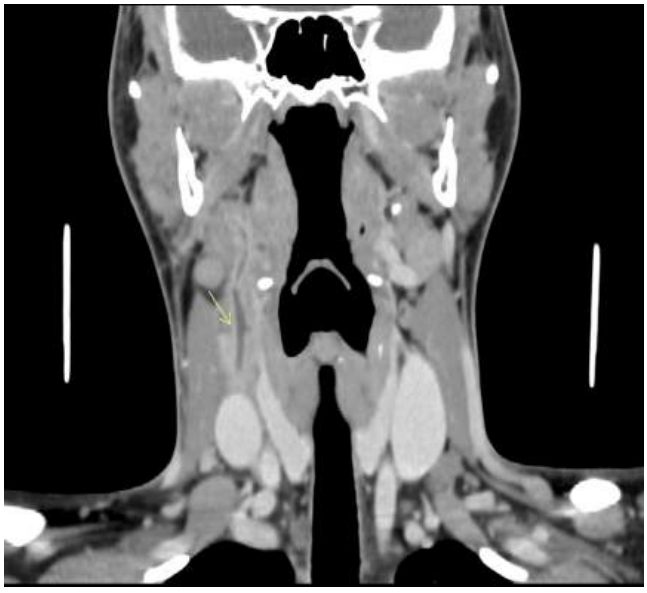

Figure 1. CT of the neck with contrast medium: a filling defect of the right facial vein is highlighted.

The patient was hospitalized in the emergency medicine ward. Antibiotic therapy with amoxicillin clavulanic acid intravenously (1000/200 mg q8h), analgesic therapy with intravenous ketoprofene 100 mg q12h, and hydration with crystalloids (1500 mL daily) were started. Over the following days, his clinical condition remained stable, but he developed nausea, vomiting, and a slight thrombocytopenia with increased total bilirubin (Table 1). On day 5, he underwent pharyngeal fibroscopy that showed acute tonsillitis with hemorrhagic area on the right tonsil, without fibrinous plaques, nor signs of phlegmon or abscesses and extreme pain when palpating the neck. A total-body CT scan with contrast medi-

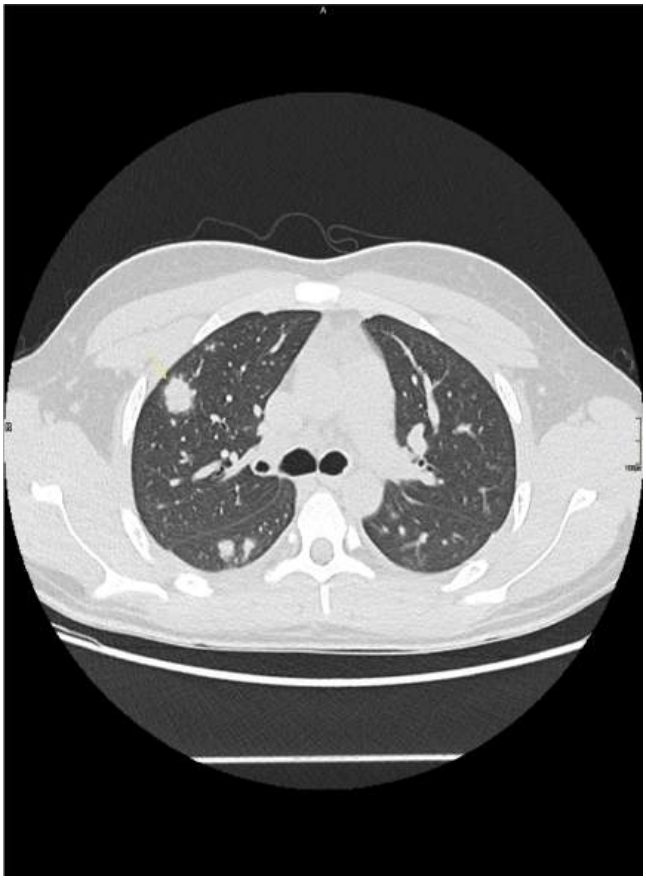

Figure 2. Chest CT showing multiple nodular parenchymal thick-right lung, expression of septic emboli.

Table 1. The patient's laboratory findings at admission and during recovery. CRP, C-reactive protein. PCT, procalcitonin. Normal values are in brackets.

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	On discharge
Leukocytes (4,5-13x10^3/mm^3)	16,810	14,870		6,490	10,150	11,560	11,430	7,620
Neutrophil (1,5-6x10^3/mm3)	15,640	13,810		4,160	7,050	8,260	7,300	4,290
CRP (<5.0 mg/L)	331	324		138	94	93	69,6	5,5
Creatinine (0.70-1.20 mg/dL)	2,05	2,02		1,04	1,04			1,12
Platelets (140–400×10^3/mm^3)	147,000	113,000		92,000	131,000		237, 000	615,000
PCT (<0.5 ng/mL)			99,20			4,66		0,22
Total bilirubin (1.20 mg/dL)	3,16					1,46		
Indirect bilirubin (mg/dL)		1,47					0,66	

um was performed revealing thrombosis of the common facial vein and its tributary branches (Figure 1), diffuse pulmonary parenchymal inflammatory nodules (maximum diameter of 2 cm; Figure 2), and bilateral renal involvement compatible with pyelonephritis (Figure 3). On day 5, the blood culture performed at admission resulted positivity for Fusobacterium necrophorum. A diagnosis of LS was finally made and the antibiotic therapy was switched to piperacillin-tazobactam (4.5 gr q6h IV) and clindamycin (600 mg q8h IV). Full-dose enoxaparin therapy was initiated subcutaneously (8000 I.U. q12h). A brain CT scan with contrast medium and an echocardiogram were performed and resulted negative. On day 6, antibiogram showed susceptibility for piperacillin-tazobactam, meropenem, clindamycin and metronidazole. According with the infectiologist, clindamycin was replaced with metronidazole (500 mg q8h iv).

We observed a gradual clinical improvement with defervescence, a progressive reduction in pharyngeal and lateral cervical pain, normalization of renal function, and a decrease in inflammatory markers to normal levels (Table 1). On day 16, the patient was discharged in full wellbeing. Two weeks later, he underwent a total-body CT scan that confirmed the complete resolution of inflammatory foci and vein recanalization.

Discussion

According to the original description, LS is characterised by pharyngotonsillitis complicating with jugular vein thrombosis and severe anaerobic septicaemia. In a minority of cases, thrombophlebitis may affect another vein in the head and neck.[4] In our patient, the thrombosis affected the facial vein and its tributary branches.

Epidemiology and aetiology

LS mainly affects young adults. A recent systematic review found a median age of 21 years (inter-quartile range Q1-Q3 =17-33)[4] with a slight male prevalence (females 41%)[4]. Several cases are described in adolescence.[2,5] It is a rare syndrome in the antibiotic era, with an increasing incidence in recent decades, resulting in 5.5 cases per million of inhabitants in 2017.[6,7] The reasons for this increase are not entirely clear. It has been hypothesized that this is due to the increase in antibiotic resistance or altered patterns in their prescriptions, as well as the decrease in tonsillectomies.[8] Furthermore, greater diagnostic accuracy comes into play with the refinement of investigation techniques.[2] Alcohol consumption and intravenous drug use has also been reported as favouring factors.[9,10]

With regard to the aetiology, up to a third of cases manifests polymicrobial bacteremia.[2] In a high percentage of cases *Fusobacterium necrophorum* is isolate. It is an anaerobic, gram-negative highly virulent bacillus, frequently isolated from the oropharingeal cavity. It appears to have vessel tropism and a tendency to activate directly the coagulation cascade and platelet aggregation.[4] It has several factors that increase its virulence including adhesins, endotoxins, leukotoxins, and hemolysins, which increase its ability to cause a necrotic abscess.[3,11] Other pathogens identified include *Fusobacterium nucleatum, Bacteroides, Streptococci, Klebsiella pneumoniae,*[12] *Eikenella corrodens,*[3] *Escherichia Coli,*[13] *Staphylococcus aureus* with recent findings of methicillin-resistant strains.[14]

Some authors have hypothesized that an alteration of the pharyngeal mucosa, caused by a bacterial or viral infection, such as infectious mononucleosis,[15] may promote the spread of the germ, which is normally non-invasive, with local dissemination in the lateral pharyngeal space, and with diffusion to the internal jugular through the tonsillar veins or the lymphatic system. In addition to the oropharyngeal origin, otomastoiditis especially in childhood, sinusitis, dental and gingival infections,[16,17] bronchopneumonia and cellulitis are described as possible sources.[2,7] Furthermore, some authors have postulated that the presence of a patent foramen ovale contributed to the arterial hematogenous spread of *Fusobacterium necrophorum* and extensive systemic embolization.[18] Thrombophilic disorders may have a role in the presentation of LS.[19]

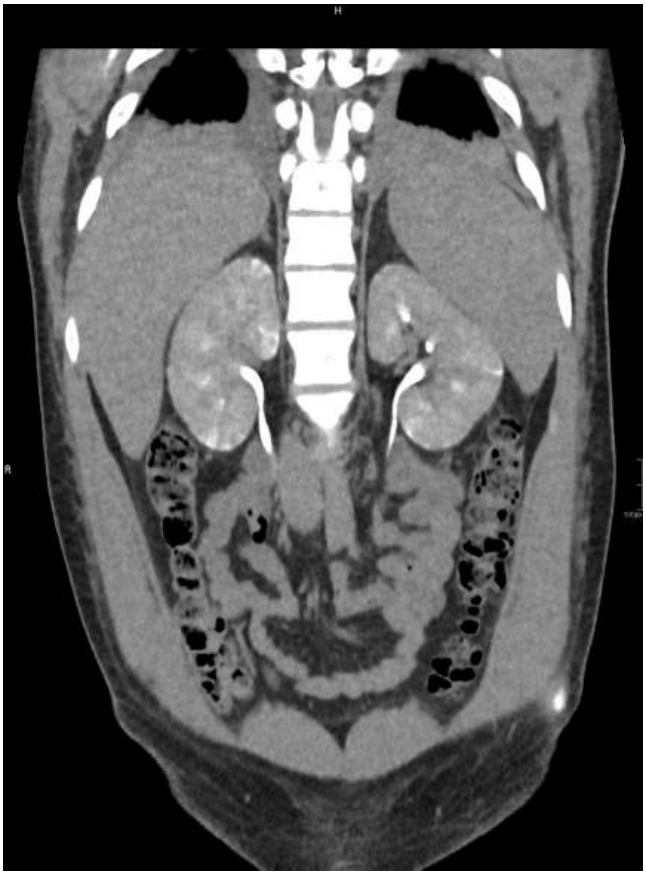

Figure 3. CT abdomen with contrast medium showing accumulation of contrast medium in the parenchyma of both kidneys compatible with pyelonephritis.

Table 2. The most typical and frequent signs and symptoms of Lemierre syndrome.

Symptoms	Signs
Pharyngodynia	Fever with chills
Laterocervical pain	Laterocervical swelling
Myalgia	Muscle stiffness
Headache	Dental infection
Cough	Purpura
Odinophagy	Jaundice
Pleuritic chest pain	
Nausea/vomiting	

Clinical presentation, course and prognosis

The signs and symptoms of LS generally appear in two stages (Table 2).[7] The first stage is a primary infection with oropharyngitis, fever with chills, and sore throat. The second stage is characterized by thrombophlebitis of the internal jugular vein or other vein in the head or neck, and sepsis, which may appear even several days after the first stage. It is important to know that signs of the previous infection can be resolved, and sepsis can mask the symptoms. Thrombophlebitis most frequently manifests with ipsilateral neck pain, headache, and laterocervical swelling.[20] It is probably the result of endothelial dysfunction caused by the inflammatory factors of the local infection.

Once septic thrombophlebitis of the internal jugular vein occurs, septic emboli can spread to different organs, mainly in the lungs with possible formation of abscesses and pleural empyema[3]. Spreads to the joints, liver and brain are also relatively frequent. Retrograde extension of septic thrombosis from the internal jugular vein can cause brain or epidural abscesses.[18] Osteomyelitis is reported in 3% of patient.[2] Endocarditis and splenic emboli are very rare. In the clinical case described, there was bilateral renal spread, which has been described so far only exceptionally.[2,4,7]

The reported mortality rate is 3-4%,[4] but it can be significantly increased if antibiotic treatment is delayed.[7] Septic shock occurs in approximately 7% of cases. Acute respiratory distress syndrome due to necrotic cavitary lesions and requiring mechanical ventilation may affect up to 10% of patients.[21]

More than 10% of patients present permanent sequelae, mainly neurological, consisting of paresis of the cranial nerves,[22] blindness, decreased visual acuity, and paresis of the limbs.[7] In a recent systematic review, thromboembolic recurrences and septic emboli were described in 14% of cases more than one month after onset.[4]

Diagnosis

The diagnosis of LS is essentially clinical, but its identification in the early stages can be a challenge, be virtually indistinguishable in its early stages from other conditions, particularly in young patients with recurrent benign oropharyngeal infections, leading to a delay in diagnosis and treatment with possible severe complications, including a poor prognosis with fatal exitus.[21] A Swedish retrospective study showed that 59% of patients were diagnosed and taken into care late.[23] Moreover, its rarity may mean that emergency physicians may not have encountered it in their practice.[7,24] In some cases, the patient's initial presentation can be confounded by an overlap SARS-CoV-2 infection.[25]

Traditionally, the key criteria for diagnosing LS are as follows:[2] i) sepsis originating from head or neck site, predominantly oropharyngeal; ii) thrombophlebitis of an internal jugular vein or other vein in the head or neck; iii) disseminated infection.

Blood tests show significant increase of inflammation indexes and may show thrombocytopenia. Assay for EBV is positive in a very small percentage of cases.[26] Blood cultures play a key role and the isolation of *Fusobacterium necrophorum* leads to the correct diagnosis. It has been speculated that cases of failure to isolate *Fusobacterium necrophorum* may be due to false negatives as it is an anaerobic gram negative.[6,7] For this reason, the use of PCR (Polymerase Chain Reaction) has been recommended in cases of negative blood cultures.[9]

With regard to diagnostic imaging, in 75% of the cases, some degree of pulmonary consolidation was shown on the X-ray, whereas 10% of the X-rays were reported as normal.[27] Total body CT scan with contrast medium is generally considered the gold standard because of its ability to visualise both internal jugular vein thrombosis and organ damage. The doppler can be used to detect thrombosis but is less sensitive than CT, especially for newly formed or subclavian thrombi.[1] MRI can be considered the most reliable technique although its use is limited by cost and availability. Compared to CT, it offers greater contrast in soft tissue, which makes it preferable in assessing neck abscesses, intracranial complications and metastases. However, it is less suitable for the evaluation of intraparenchymal lung lesions.[1]

Therapy

Antibiotic therapy is the mainstay of LS treatment. Metronidazole is particularly effective in the treatment of *Fusobacterium necrophorum* and is usually combined with carbapenems or penicillins, especially piperacillin/tazobactam.[2,3,7,19] The combination is strongly recommended, given the high frequency of mixed infections.[23,7] *Fusobacterium necrophorum* is usually sensitive to penicillins, although recently beta-lactamase-producing strains have been isolated. It is also usually sensitive to cephalosporins, clindamycin, and chloramphenicol.[19] It is naturally resistant to quinolones and aminoglycosides.[28] It has dubious sensitivity to macrolides and tetracyclines.[19,28] If CNS involvement is suspected, vancomycin, ceftriaxone, and metronidazole are recommended.[3] The average duration of antibiotic treatment should be at least 3 weeks. Haemodynamic support may be required with fluid resuscitation and vasoactive agents (e.g., norepinephrine) ensuring end organ perfusion.[3]

Surgical treatment may sometimes be necessary for drainage of abscess collections, pleural empyema, and debridement of necrotic material.[29]

The indication for the use of anticoagulants appears controversial, and more than half of the patients receive anticoagulant therapy at different dosages.[4] This may be due to the perceived unacceptable risk of increased bleeding and the fear that the anticoagulant may fragment the thrombus and cause new septic lesions. The studies performed showed no significant differences in the main outcomes, or in the occurrence of major bleeding, between patients treated and those not treated with anticoagulants.[6,30] These studies are either retrospective or of limited size. It is the opinion of some authors that anticoagulant therapy should be adopted in the absence of contraindications as it can contribute to reducing the risk of relapses.[4] It is likely that the bacteria within the thrombus may be less exposed to the action of the antibiotic and therefore a more rapid dissolution of the thrombus may help to treat the infection advantageously.[4,7,31] It may be plausible to consider 6 to 12 weeks as the ideal anticoagulation window.[32] Two case reports lend support to the use of direct oral anticoagulants.[32]

Conclusions

Emergency clinicians should consider LS in all the young patients who develop sepsis following a sore throat resistant to antibiotics. LS is a rare but life-threatening condition that can trigger a thrombotic and inflammatory response, potentially leading to multi-organ failure with a poor prognosis if not promptly identified and treated. Although the disease appears to be more common nowadays – possibly due to improved diagnostic sensitivity – its overall rarity has limited extensive and structured studies. However, there has been a gradual increase in the number of recent studies in the literature, including reviews and case reports. These

works focus on vital aspects such as diagnostic suspicion, therapeutic management, and outcomes. In most cases, outcomes are favourable without significant long-term effects, as long as treatment is timely and appropriate.

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