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Editorial

LEMIERRE'S SYNDROME: THE FORGOTTEN DISEASE IS ON THE RISE

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Lemierre's syndrome (LS), also known as post-anginal sepsis and necrobacillosis, is a rare life threatening multisystemic infection, begins with acute oropharyngeal suppurative infection (bacterial pharyngitis/tonsillitis) causing persistent bacteremia and involves an extension of the infection into the lateral pharyngeal spaces of the neck with subsequent septic thrombophlebitis of the internal jugular vein, and metastatic lung lesions in the form of septic emboli, thrombotic extension to the CNS. Since the LS is rare, diagnosis is often delayed increasing the morbidity and mortality.[1] This article is written in recognition of the importance of raising the awareness about rare diseases, and aims to educate readers about Lemierre's syndrome, emphasizing its clinical features, including oropharyngeal infections and thrombophlebitis, as well as challenges in diagnosis.

LS took its name after the French bacteriologist Andre-Alfred Lemierre, who first described the syndrome in 1936.In 1980 that Vogel and Boyer defined a syndrome that they named Lemierre's postanginal septicemia. In 1983, Shannon et al. was the first author to refer to this syndrome as Lemierre's syndrome. The disease was widespread before the invention of antibiotics and had a fatal course (90%) within one to two weeks. With the discovery of antibiotics, and with the use of penicillin in the 1960s and 1970s, the cases of LS declined sharply. It was referred to as a "forgotten disease" in the 1980s and 1990s due to remarkable drop in published reports of this disease. However, since the late 1990s, there has been a rise in LS cases, and the last 15 years have witnessed a remarkable increase in the reported cases.[2] It may be due to restricted use of antibiotics for upper respiratory tract infections as per antibiotic stewardship recommendations. Beta-lactams are indicated only in group A streptococcal pharyngitis or suppurative tonsillitis. The use of macrolides, fluoroquinolones have increased in the past decade. *Fusobacterium necrophorum* is intrinsically resistant to macrolides, fluoroquinolones, tetracyclines, and aminoglycosides.[3,4]

ETIOLOGY

LS is usually caused by obligate anaerobic Gram negative bacilli, and other facultative anaerobic bacteria.

The most commonly responsible bacteria are Fusobacterium necrophorum, followed by Fusobacterium nucleatum. Lipopolysaccharides of Fusobacterium necrophorum have endotoxic properties and are important virulence factors. Other causative organisms include beta hemolytic streptococci, Streptococcus anginosus and Streptococcus intermedius (both of them are alpha hemolytic or viridians streptococci or Streptococcus milleri group), Bacteroides species, Veillonella parvula (anaerobic Gram negative coccus), Gemella species (anaerobic Gram positive coccus), Staphylococcus aureus, and MRSA, Enterococcus, Proteus,and Klebsiella pneumoniae. Other pathogens such as Epstein-Barr virus, Influenza virus, Cytomegalovirus, Mycoplasma pneumoniae may contribute to infection associated mucosal damage and disease progression.[5,6]

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PATHOGENESIS

Fusobacterium necrophorum is a part of the normal bacterial flora in the oropharynx, gastrointestinal tract, and female genital tract.[5] LS usually presents as a sore throat, and pharyngitis is the entry source for more than 85% of cases, while otitis media or dental infection accounts for <2% of cases. The infection extends from the oropharynx into the lateral pharyngeal space and soft tissues of the neck by anaerobic oral pathogens. Venous thrombosis is initiated locally in the peritonsillar veins and then results in the seeding of the internal jugular vein. Fusobacterium necrophorum has been shown to aggregate human platelet in vitro, subsequently precipitating intravascular coagulation. This may lead to septic thrombophlebitis, and subsequent access to the venous system, resulting in septicemia and septic emboli.

The release of septic emboli into the systemic circulation results in the widespread dissemination of Fusobacterium necrophorum into the lung, pleura, joints, bones, muscles, spleen, liver, kidney, and other endpoints of circulation causing metastatic abscesses.[7-9]

CLINICAL FEATURES

The clinical presentation and progression of LS can be divided into 3 main classical stages.

1. **Primary infection of oropharynx**: The clinical features of LS begin with an oropharyngeal infection (prolonged sore throat/pharyngitis) with fever and rigors anywhere from 4 to 7 days after the initial illness. Early diagnosis of LS is difficult, since symptoms are non-specific, and may be confused with parotitis, mastoiditis, sinusitis, and dental infections. The persistence of fever and worsening clinical status at one week can be an important clue.[7,10]
2. **Lateral pharyngeal space tissue invasion**: Infection extending to the parapharyngeal space of the neck with thrombophlebitis of the internal jugular vein. neck tenderness and swelling may be an early clinical sign when pharyngitis extends beyond the oropharynx. Unilateral tenderness and swelling at the mandibular angle, known as the "cord sign" indicates internal jugular thrombosis.[8,11]
3. **Metastatic spread/Septic emboli**: It occurs when *Fusobacterium necrophorum* invades cervical veins. The most frequently affected organ is the lungs (85%), but joints, liver, kidney, bones, heart, brain, and meninges can all be involved. Pneumonia or pleual empyema is the most common metastatic infection. Hepatic involvement may present as jaundice, abdominal pain and hepatomegaly with abscesses. Hyperbilirubinemia may be either due to liver abscesses or a direct effect of the toxin on biliary tree. Joint and bone involvement may present as septic arthritis or osteomyelitis. Direct extension or propagation of thrombus can result in CNS abscess formation as well as cavernous sinus thrombosis. Atypical sites of infection associated with LS have been reported in the abdomen, often in association with urogenital infections or with pelvic infections. Septic shock occurs approximately in 7% cases and acute respiratory distress syndrome requiring mechanical ventilation may affect up to 10% cases.[8-12]

DIAGNOSIS

A definitive diagnosis of LS should be made based on a recent pharyngitis (sore throat), clinical or radiographic evidence of thrombophlebitis of the internal jugular vein, as well as septic emboli, and isolation of an anaerobic pathogen, *Fusobacterium necrophorum* in blood cultures or from other infected sites. Blood cultures may be negative due to difficulties associated with cultivation of anaerobic bacteria. The main components of the diagnosis are the examination of the systemic inflammatory response syndrome criteria, abnormal liver function tests including elevated bilirubin, thrombocytopenia, leukocytosis, elevated CRP, as well as other evidence of disseminated intravascular coagulation. Since the lungs are the most common site of metastatic infection, a chest radiograph to evaluate for septic emboli and other pulmonary complications, including pulmonary effusions, lung abscesses, and empyema should be included in imaging. Magnetic resonance imaging (MRI). ultrasound, CT of the neck with contrast may also be performed to test for septic thrombosis of the internal jugular vein, and other complications such as pulmonary emboli, empyema, lung abscesses.[11-13]

TREATMENT & MANAGEMENT

The mainstay for treatment for LS is antibiotic therapy. Antibiotics should be tailored to the culture results and antibiotic susceptibility data when available. A beta-lactamase resistant beta-lactam antibiotic is recommended as an empirical therapy due to case reports of treatment failures with penicillin. Alternative options include clindamycin or metronidazole for patients with allergy to beta-lactams. Antibiotic therapy should be continued for 6 weeks in most cases to achieve appropriate penetration into fibrin clots.[3,4]

Surgical management may be necessary in cases of abscess formation, respiratory distress secondary to pulmonary thrombosis, metastasis, and in patients with extension of thrombus into the mediastinum or cerebrum. Surgical incision and drainage of the abscess at affected sites may be indicated to control infection.[7,9]

Anticoagulation treatment for LS is controversial and carries the risk of extending the infection. Uncomplicated LS without evidence of extensive clot burden resolves with appropriate antibiotic therapy and supportive care and does not require anticoagulation. The best anticoagulation therapy has not been determined by randomized clinical trials. However, anticoagulation therapy is usually recommended when the thrombus extends into the cerebral sinuses, for large or bilateral clot burden, or when a patient fails to improve in the first 72 hours with appropriate antibiotic and/or surgical therapy.[14,15]

Advanced LS is a life threatening condition. Hospital admission usually requires ICU status. Even with appropriate antibiotics and therapy, mortality rate has been reported to be between 5% and 18%.[3,12]

CONCLUSION

If not treated and recognized early, LS is a life threatening complication of oropharyngeal infection, typically affecting young, previously healthy adolescents, and young adults between 10 to 35 years of age. LS is a rare condition characterised by a triad of sepsis, thrombophlebitis of the internal jugular vein along with pleuropulmonary and/or distant metastatic abscesses. The unwary clinician may easily overlook its diagnosis. Clinicians should be vigilant and suspect LS when symptoms of pharyngitis do not improve over the course of few days, and systemic signs develop after a pharyngeal infection, particularly in young patients, especially if there are signs of metastatic infection, most commonly in the lungs. It is recommended that LS should be considered in the differential diagnosis in patients presenting with persistent sore throat, mastoiditis, recent history of a dental procedure, and/or signs of active gingivitis, accompanied with neck pain and swelling. The disease course is rapid and irreversible therefore, timely diagnosis and prompt antibiotic therapy are crucial for the good prognosis.

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