A Review Of Lemierre Syndrome

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Citation

Abstract

Lemierre syndrome (postanginal septicemia) is caused by an acute oropharyngeal infection with secondary septic thrombophlebitis of the internal jugular vein and frequent metastatic infections. A high degree of clinical suspicion is necessary for diagnosis. Fusobacterium necrophorum (F necrophorum) is the usual etiologic agent.

The disease progresses in several steps. The first stage is the primary infection, which is usually a pharyngitis. This is followed by local invasion of the lateral pharyngeal space and Internal Jugular Vein (IJV) septic thrombophlebitis, and finally, the occurrence of metastatic complications. A sore throat is the most common symptom during the primary infection. During invasion of the lateral pharyngeal space and IJV septic thrombophlebitis, a swollen and/or tender neck is the most common finding and should be considered a red flag in patients with current or recent pharyngitis. The most common site of metastatic infection is the lungs. In contrast to the preantibiotic era, cavitating pneumonia and septic arthritis are now uncommon. Most patients had fever at some stage during the course of the disease.

We conclude that the typical course of the disease has changed since Lemierre's original description most likely as a consequence of widespread antibiotic use for pharyngeal infections. Mortality is low now a days, but significant morbidity still occurs, which is likely preventable by early diagnosis and treatment. The pathophysiology, natural history, diagnostic methods for internal jugular vein thrombosis, and management are discussed here.

INTRODUCTION

Lemierre syndrome, also known as postanginal sepsis or necrobacillosis, is an uncommon but potentially life-threatening complication of acute pharyngotonsillitis. Anaerobic oropharyngeal infection may result in septic thrombophlebitis of the ipsilateral internal jugular vein with subsequent septicemia and septic embolization, which cause metastatic abscesses, commonly in the lungs and less commonly in the large joints. In 1936, Lemierre [1] gave a detailed description of the condition reported by Schottmuller in 1918 that came to bear Lemierre's name and indicated that the clinical findings were "so characteristic that mistake is almost impossible." In the preantibiotic era, Lemierre syndrome was common and often followed a fulminant course, with a mortality rate of 90% [1]. In recent years, the widespread use of antibiotics in the management of acute oropharyngeal infection has led to a rapid decline in the prevalence of Lemierre syndrome. Lack of familiarity with this condition, which patients may have when they present to the ear, nose, and throat surgeon, physician, or pediatrician, can lead to serious delay in diagnosis and may explain why it has been referred to as "a forgotten disease" [2].

Over the past 2 decades, occasional case reports and literature reviews pertaining to Lemierre syndrome have been published in the medicine, pediatrics, and otorhinolaryngology literature [2,3,4,5,6,7,8,9,10,11]. The purpose of this review is to heighten physician's awareness of this syndrome to expedite diagnosis of a syndrome that often manifests as nonspecific clinical and chest radiographic findings.

ETIOLOGY AND PATIENT CHARACTERISTICS

Most cases occur in patients aged 16–25 years, but cases occasionally occur in younger patients and older patients as well. Most patients are previously healthy individuals. The etiology of Lemierre syndrome is found to be Fusobacterium necrophorum (F. necrophorum) in 81.7% of the cases, as demonstrated by positive cultures from clinical specimens, usually blood. However, several other organisms are found to be reported, alone (5.5%) or in combination with F.

necrophorum (10.1%). These include Bacteroides asaccharolyticus, Bacteroides fragilis, Bacteroides gracilis, Bacteroides melaninogenicus, Bacteroides distasonis, Bacteroides uniformis, Peptostreptococcus, Group B and C Streptococcus, Streptococcus oralis, Staphylococcus epidermidis, Enterococcus sp., Proteus mirabilis, Eubacterium sp., Eikenella corrodens, lactobacilli, and Candida sp. Cultures are negative in 12.8% of cases. [12]

PATHOGENESIS

F. necrophorum has an unusual ability to cause severe disease as a primary pathogen in previously healthy people with intact anatomical barriers [19, 21, 23, 26,27,28,29], unlike other anaerobic bacteria. The disease progresses in several steps. The first stage is the primary infection, which is usually pharyngitis [19, 21, 23, 26,27,28,29]. This is followed by local invasion to the lateral pharyngeal space and internal jugular vein (IJV) septic thrombophlebitis, and finally, the occurrence of metastatic complications.

In the majority of cases, a temporal pattern is obvious in that these stages occur in an orderly fashion and correspond to distinct clinical manifestations. [12] Below, the pathophysiology of each stage is reviewed:

PRIMARY INFECTION

The palatine tonsils and peritonsillar tissue are found to be the primary source of infection in most cases (87.1%). Odontogenic infections (1.8%) and mastoiditis (2.7%) also occur in some patients. Additional sources have been reported in other series, including parotitis, sinusitis and primary infection in the skin or subcutaneous tissues of the head and neck. [12]

The clinical findings in this stage depend on the primary site of infection. Since pharyngitis made up the vast majority of cases, a sore throat and evidence of pharyngeal inflammation are the primary findings. Fever occurs in about 82.5% of cases, but not necessarily at the time of initial presentation. Gastrointestinal complaints such as abdominal pain, nausea, and vomiting are present in 49.5% of cases. At this point in presentation, there are no "red flags" that would suggest the etiology. Many patients have only subtle findings, such as hyperemia of the pharynx.

The percentage of cases of F. necrophorum pharyngitis that progress to invasion of the lateral pharyngeal space and IJV septic thrombophlebitis is unknown. [12, 22]

The time interval between the oropharyngeal infection and the onset of the second stage is usually less than 1 week. In some cases, signs and symptoms related to oropharyngeal infection have cleared (at times without antibiotic therapy) by the time IJV thrombosis developed. [12]

INVASION OF THE LATERAL PHARYNGEAL SPACE AND IJV THROMBOPHLEBITIS

In the past, it was thought that IJV thrombophlebitis was initiated in the tonsillar and peritonsillar veins with subsequent spread to the IJV. However, it is likely that the most common mechanism involves spread of infection from peritonsillar tissue to the adjacent lateral pharyngeal space, mainly via lymphatic vessels [18]. It is the infection of this compartment that can cause complications such as thrombophlebitis of the IJV and severe sepsis with metastatic infections [19, 21, 23, 26,27,28,29].

The lateral pharyngeal space is divided by the styloid process into an anterior (muscular) and a posterior (neurovascular) compartment. The posterior neurovascular compartment includes the IJV, the carotid artery, the vagus nerve, lymph nodes, cranial nerves X-XII, and the cervical sympathetic trunk. The clinical findings of the invasion of this compartment result from compromise of these vital structures.

Carotid artery rupture has occurred and is the most catastrophic complication of this stage; Horner syndrome may occur if the sympathetic trunk is involved. Paralysis of the trapezius muscle has been reported, most likely secondary to compromise of the spinal accessory nerve [3]. Dysphagia occurs in 17.4% of patients. The most frequent finding (52.2%) at this stage is a tender and/or swollen neck, and this should be considered a warning sign in a patient with pharyngitis. The pain and swelling may extend from the angle of the jaw and along the sternocleidomastoid muscle, sometimes with associated trismus (9.1%) [13, 15, 17, 28, 30,31,32]. Pain when turning the head away from the involved site may occur as a consequence of irritation of the sternocleidomastoid muscle. Spasm of the sternocleidomastoid muscle may occur as well. The thrombosed jugular vein is rarely palpable. It must be remembered that local findings may be subtle or absent, particularly if the infection selectively affects the posterior compartment of the lateral pharyngeal space. No significant neck findings are present in 47.7% of the patients. [12]

METASTATIC COMPLICATIONS

Once the infection involves the IJV, it may cause bacteremia

with hematogenous spread to other sites. The first sign of this complication may be fever, soon thereafter accompanied by intense rigor. The lungs are by far the most common metastatic target (79.8%), followed by the joints (16.5%). The typical pulmonary findings in Lemierre syndrome reported previously are those resembling septic pulmonary embolism with chest X-ray findings of cavitating pneumonia, similar to what is seen in right-sided bacterial endocarditis with septic embolization. Associated pleural effusions are common (43.1%) and may precede the appearance of pulmonary infiltrates. A normal chest X-ray is present in 19.2% of cases, and only 31.1% of patients had radiologic evidence of cavitation. Empyema and lung abscess may be seen, and both pneumatoceles and pneumothorax have been described. Frank respiratory failure requiring ventilatory support occurs in 15.5% of cases. ([12])

The second most common sites of septic embolization are the joints, with the hip, shoulders, and knees most frequently involved ([10, 15, 20, 24,25,26]). The frequency of joint involvement is 16.5% now, significantly lower than in the preantibiotic era (66.6%). Other sites of septic dissemination include hepatic or splenic abscesses (2.7%). However, splenomegaly and hepatomegaly are common (15.5%) and are not necessarily associated with liver or hepatic abscesses ([24]). Mild hyperbilirubinemia with slight elevation of liver enzyme levels has been reported to be a common finding ([8]). Renal involvement with proteinuria and hematuria has been described as the predominant manifestation in a patient ([14]). When renal complications develop, the syndrome may be mistaken for poststreptococcal glomerulonephritis. Metastatic spread of infection through embolization complicated all the cases described by Lemierre. However, this seems to be preventable by early antibiotic treatment ([16, 25])

OUTCOME

In the cases described by Lemierre in the preantibiotic era, the outcome was fatal with rapidly progressing septicemia ([16, 25]). The outcome of the syndrome after appropriate therapy has been instituted is favorable in most patients, although adult respiratory distress syndrome has been reported, and fatal cases have been seen even in the antibiotic era. Clearly, however, if it is recognized and appropriately treated, Lemierre syndrome has a good prognosis in most cases. ([12])

DIAGNOSIS

Lemierre himself stated ([25]) that: The appearance and repetition several days after the onset of a sore throat (and particularly of a tonsillar abscess) of severe pyrexial attacks with an initial rigor, or still more certainly the occurrence of pulmonary infarcts and arthritic manifestations, constitute a syndrome so characteristic that mistake is almost impossible.

In fact, the diagnosis of Lemierre syndrome on the basis of clinical grounds should be considered if the physician is aware of the existence of the disease. However, it is rare today and has been said to be "forgotten" by the medical community ([13, 24, 27, 28,31]). Most patients have evidence of metastatic complications by the time of diagnosis. ([12])

MANAGEMENT

The approach to a patient with pharyngitis and a tender/swollen neck should be aggressive. Blood cultures should be obtained, evidence of IJV thrombophlebitis should be sought, and anaerobic coverage with metronidazole or clindamycin should be initiated. Diagnostic methods to detect IJV thrombophlebitis include Computed Tomography (CT) scan, Magnetic Resonance Imaging (MRI) and ultrasound.

Ultrasound, the least expensive, may reveal an echogenic region within a dilated jugular vein, or a complex mass of solid and cystic components. However, it may miss a fresh thrombus with low echogenicity, and imaging the area beneath the clavicle may be technically difficult. CT scans are better able to demonstrate the anatomy and the presence of abscesses that need to be drained. This method may also reveal low attenuation intraluminal filling defects, and adjacent soft tissue swelling.

Some authors have recommended CT as the primary diagnostic method, with ultrasound being the best test for follow-up once the anatomy has been well defined. If the patient has infection arising from the mastoid, the presence of intracerebral vein thrombosis specifically needs to be excluded (usually with MRI). ([33,34,35,36,37,38,39,40,41,42])

For the treatment of Lemierre syndrome today, we certainly have more tools than Lemierre had at his disposal. The only recognized treatment in the preantibiotic era was ligation of the IJV on the affected side in an attempt to prevent septicemic spread. Today, the mainstay of treatment is prolonged antibiotic therapy (4–6 weeks), which seems necessary to eradicate the infection, probably because of its endovascular nature. F necrophorum is usually susceptible in vitro to penicillin, clindamycin, or metronidazole. ([43, 44]) However, deaths caused by a β-lactamase–producing strain

have been reported. ($_{45}$) In addition, data indicate an increasing resistance to erythromycin, commonly used for empirical antimicrobial treatment of oropharyngeal infections. A study of cases during 1990-2000 showed that, although F necrophorum isolates remain fully susceptible to metronidazole, resistance to penicillin was 2% and to erythromycin was 15% in all isolates. This observation may be of potential clinical relevance because it could partly account for the perceived increase in the incidence of Lemierre syndrome in recent years. ($_{46}$)

Considering the devastating consequences that result frequently from this infection, we suggest initial empirical therapy for suspected or confirmed F necrophorum sepsis and Lemierre syndrome with a β-lactamase–resistant antimicrobial agent until results of antimicrobial susceptibility tests are available. The duration of antibacterial therapy should be prolonged; most patients should be treated for at least 4 to 6 weeks.

Use of anticoagulant therapy for necrobacillosis-associated thrombosis is controversial. Because the illness is rare, no published data have assessed the efficacy of anticoagulation. Some experts argue against its use because of the potential risk of facilitating the spread of infection. However, others have advocated its use on the basis of data from gynecological literature that support the use of heparin for treatment of pelvic septic thrombophlebitis, especially in patients with progressive clot propagation or with embolization despite adequate antimicrobial therapy. Finally, in patients with uncontrolled sepsis and ongoing evidence of septic emboli despite appropriate medical therapy, surgical ligation or excision of the IJV should be considered. Fortunately, this treatment is rarely needed today. ($_{47,48}$)

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