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Pediatric otolaryngology: principles and practice

Lemierre syndrome: a pediatric case series and review of literature

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Abstract

Background: Lemierre syndrome is a rare disease of the head and neck often affecting adolescents and young adults. Classically, infection begins in the oropharynx with thrombosis of the tonsillar veins followed by involvement of the parapharyngeal space and the internal jugular vein. Septicemia and pulmonary lesions develop as infection spreads via septic emboli. Although a rare entity in modern times, Lemierre syndrome remains a disease of considerable morbidity and potential mortality.

Methods: This was a retrospective review of 3 cases and associated literature.

Results: A common 1- to 2-week history of fever, sore throat, neck pain, and fatigue was observed in all patients. Patient 1 developed right facial swelling, neck tenderness, trismus, and tonsillar exudate. Patient 2 displayed right tonsillar erythema and enlargement with right neck tenderness. Patient 3 revealed bilateral tonsillar enlargement with exudate and left neck tenderness. Subsequent studies included blood cultures and computed tomography, after which empiric antibiotic therapy was started. Patient 1 underwent drainage of a right peritonsillar abscess, right pressure equalization tube placement, and ligation of the right external jugular vein. He subsequently developed subdural empyemas, cavernous sinus thrombosis, and carotid artery narrowing and required 9 weeks of antibiotic therapy. Patients 2 and 3 developed pulmonary lesions and received 6 weeks of antibiotic therapy. Timing was crucial in all cases.

Conclusions: Lemierre syndrome is a rare but severe opportunistic infection with poor prognostic outcomes if left untreated. Early diagnosis and treatment is essential. Aggressive antibiotic therapy coupled with surgical intervention, when necessary, provides excellent outcomes.

1. Introduction

Lemierre syndrome, also known as postanginal septicemia or human necrobacillosis, is a rare disease of the head and neck that often affects healthy adolescents and young adults. Initially described in 1900 by Courmont and Cade [1] and again in 1918 by Schottmuller [2], it was not until 1936 when the French microbiologist Dr Andre Lemierre best characterized the disease process that now bears his name [3]. In a case series of 20 patients, Dr Lemierre described the development of septic thrombophlebitis of the tonsillar and peritonsillar veins secondary to pharyngotonsillitis or peritonsillar abscess formation. The rapidly progressive thrombophlebitis would then spread to involve the internal jugular and facial veins with the subsequent development of metastatic emboli to the respiratory tract and ultimately the remaining end points of circulation [3]. During the pre-

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antibiotic era, Lemierre syndrome was a frequent complication of head and neck infections in which nearly all patients died of overwhelming sepsis within 7 to 14 days [4].

Since the advent of antimicrobial therapy, and routine use of penicillin in the treatment of oropharyngeal infections, the incidence of Lemierre syndrome has been in steady decline. Because of the infrequency of this once common clinical disease, initial patient evaluations may not include this syndrome as a potential diagnosis [5,6]. In an effort to emphasize the importance of early diagnosis and treatment of this once "forgotten disease," we present 3 pediatric patients with Lemierre syndrome and provide a comprehensive review of current literature.

2. Materials and methods

The medical records of 3 pediatric patients diagnosed with Lemierre syndrome at 2 urban tertiary care teaching hospitals were analyzed. Data presented include clinical and laboratory findings.

3. Results

A common 1- to 2-week history of fever, sore throat, neck pain, and fatigue was observed in all patients. Patient 1 developed right facial swelling, neck tenderness, trismus, and tonsillar exudate. Patient 2 displayed right tonsillar erythema and enlargement with right neck tenderness. Patient 3 revealed bilateral tonsillar enlargement with exudate and left neck tenderness. Subsequent studies included blood cultures and computed tomography, after which empiric antibiotic therapy was started. Patient 1 underwent drainage of a right peritonsillar abscess, right pressure equalization tube placement, and ligation of the right external jugular vein. He subsequently developed subdural empyemas, cavernous sinus thrombosis, and carotid artery narrowing, and required 9 weeks of antibiotic therapy. Patients 2 and 3 developed pulmonary lesions and received 12 and 6 weeks of antibiotic therapy, respectively. Timing was crucial in all cases.

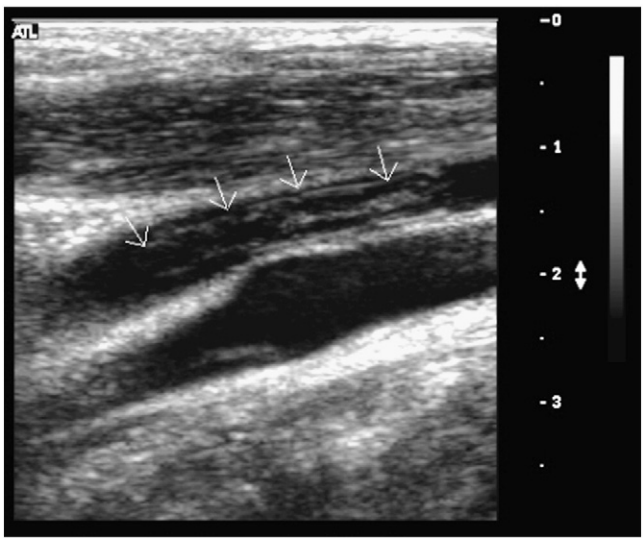

Fig. 1. Ultrasound of right internal jugular vein thrombus.

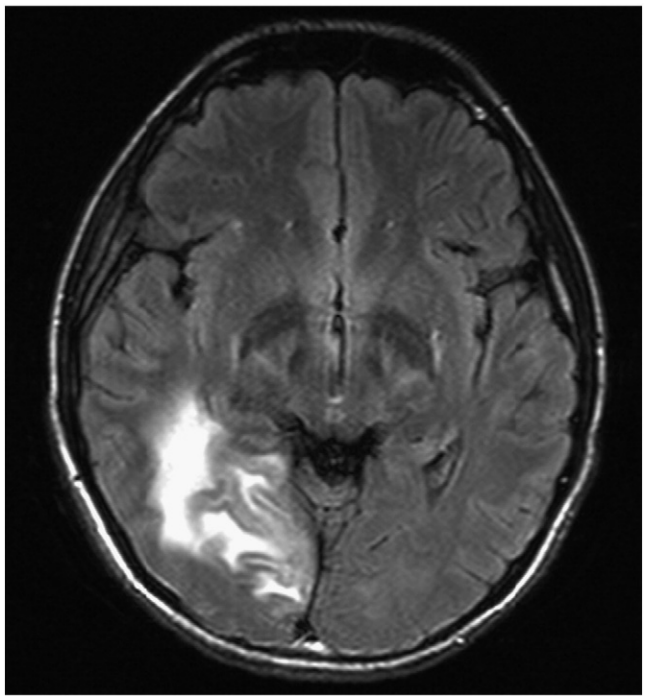

Fig. 2. Axial T1 MRI of leptomeningeal enhancement of the medial occipital lobe secondary to adjacent tentorial subdural empyema.

3.1. Case 1

A 16-year-old adolescent boy was evaluated with a 1-week history of fever, sore throat, right neck pain, decreased appetite, right facial swelling, and right eye ptosis. On admission, the patient was found to have a white blood cell (WBC) count of 22.3, hemoglobin level of 14, hematocrit of 39, platelet value of 10, and a C-reactive protein of higher than 20. The patient was empirically started on clindamycin, ceftriaxone, and azithromycin after obtaining blood cultures. Computed tomography of the head and neck was performed revealing a right peritonsillar and parapharyngeal abscess, right mastoiditis, and the suspicion of thrombosis of the right internal jugular vein. This was confirmed with ultrasound (Fig. 1). Computed tomographic (CT) angiogram of the neck was performed to define the limits of the thrombosis and evaluate the arterial system. With thrombosis limited to right internal and external jugular veins, the patient was taken to the operating theater; and a right tonsillectomy, drainage of the right parapharyngeal abscess, and placement of a right pressure equalization tube were performed. Cultures were sent for Gram stain, anaerobic, aerobic, acid fast bacteria, and fungal evaluation. Lovenox (Sanofi-Aventis, Bridgewater, NJ) was started postoperatively at 50-mg dosing.

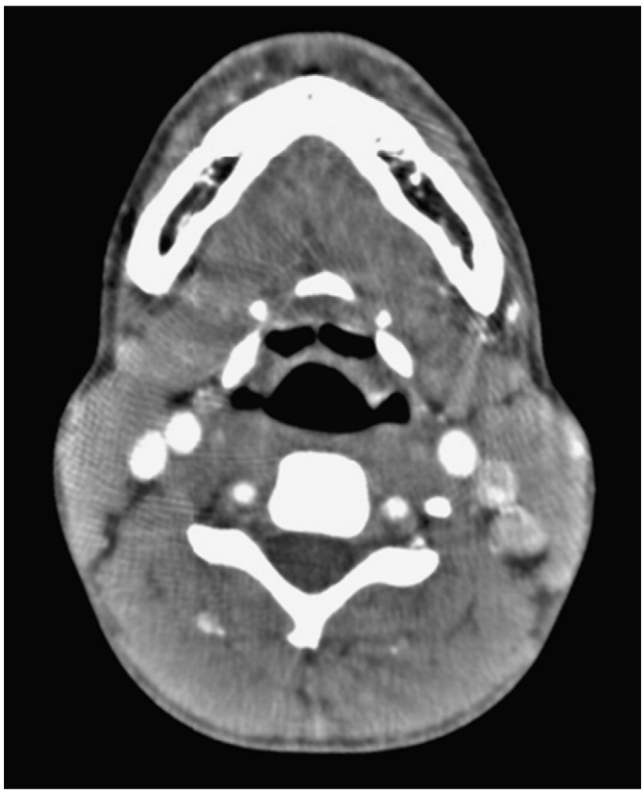

Fig. 3. Axial CT with contrast revealing left internal jugular vein thrombus.

During the patient's hospital course, he developed septic emboli to the lungs, narrowing of the right internal carotid artery (ICA) cavernous segment, and a subdural empyema (Fig. 2). At this time, blood cultures were found to be positive for *Fusobacterium necrophorum*, and antibiotic therapy was modified to ceftriaxone and Flagyl (Pfizer, New York, NY). With the patient developing meningeal symptoms, a lumbar tap was performed with cerebral spinal fluid revealing a WBC count of 65. Vancomycin was added to the antibiotic regimen. Serial magnetic resonance imaging (MRI) studies were performed revealing the stabilization of the subdural collection and cavernous ICA narrowing. Conservative therapy was once again modified to ceftriaxone, Flagyl, and penicillin G after a repeat cerebrospinal fluid study revealed increased protein and a WBC count of 85. During the remainder of the patient's hospitalization, serial MRI studies revealed gradual resolution of his cerebral, neck, and mastoid disease. However, marked narrowing of the cavernous ICA persisted. The patient was discharged on IV antibiotic of ceftriaxone and penicillin G for a period of 5 weeks.

Fourteen months later the patient presented with a 2-day history of left sore throat, fever, and neck pain. The patient immediately underwent CT evaluation of the head, neck, and chest, which revealed thrombosis of the left internal jugular vein (Fig. 3). The patient was empirically started on ceftriaxone, Flagyl, penicillin G, and Lovenox while waiting for the results of blood cultures. Once again the cultures were positive for *F necrophorum*. The patient was discharged after 4 days of hospitalization and underwent an additional 4 weeks of antimicrobial therapy.

3.2. Case 2

A previously healthy 10-year-old boy presented to her primary care provider with a 3-day history of fever, otalgia, otorrhea, and scleral icterus. Because of the severity of the patient's symptoms, she was sent to the emergency department with concerns of sepsis vs meningitis. On initial evaluation, the patient was found to be lethargic with a temperature of 103.6°F. The remaining vital signs were stable. Initial laboratory studies included a complete blood count, chem 7, blood cultures, and a liver panel. The patient was found to be neutropenic with a count of 3,

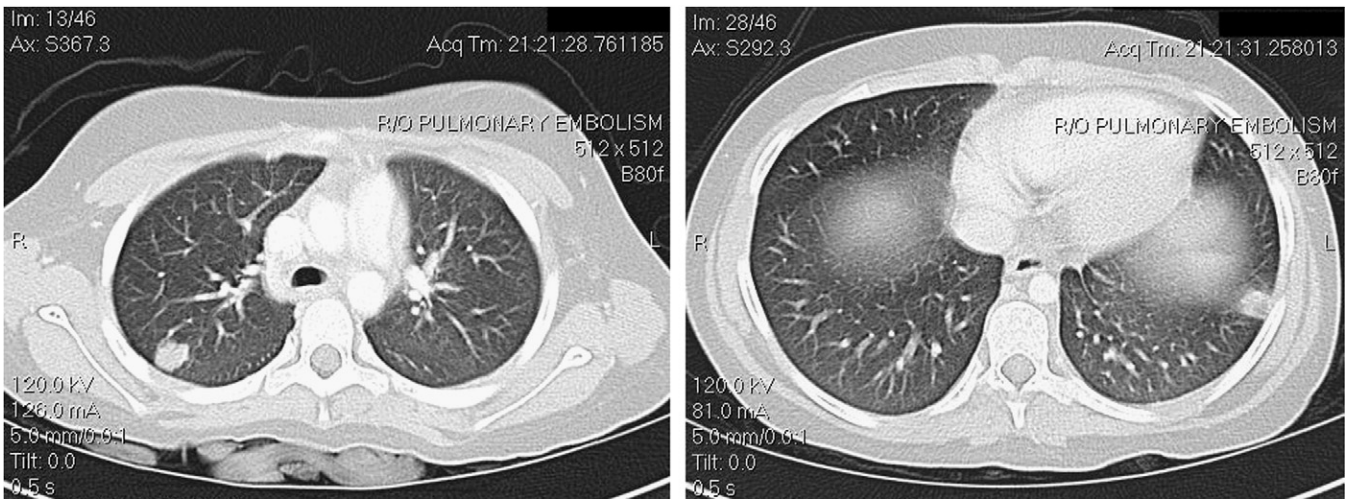

Fig. 4. Series: Axial CT images of the chest with contrast showing opacification of bilateral mastoid processes, bilateral enlarged cervical lymph nodes, and multiple pulmonary nodules.

thrombocytopenic with platelets count of 56, as well as multiple abnormalities in her liver panel with a total bilirubin of 5.3, direct bilirubin of 3.9, aspartate aminotransferase of 69, alanine aminotransferase of 45, and a gamma-glutamyl transpeptidase at 147. Physical examination revealed jaundice, left ear otorrhea, 3+ right tonsil, and diffuse right cervical lymphadenopathy.

An extensive workup was performed including cerebrospinal fluid studies and culture, monospot testing, hepatitis panel, urinalysis and culture, varicella reactive protein, cytomegalovirus, Epstein-Barr panel, and abdominal ultrasound. Computed tomography of the head, neck, and chest were also obtained and revealed opacification of bilateral mastoid processes, bilateral enlarged cervical lymph nodes, and multiple pulmonary nodules (Fig. 4). The patient's empiric antibiotic therapy was changed from ceftriaxone to meropenem at this time. Subsequent Doppler ultrasound was negative for internal jugular vein thrombosis.

Despite the absence of jugular thromboses on CT and ultrasound, it was felt that this patient most likely represented a case of Lemierre syndrome. This was later confirmed by the initial blood cultures obtained in the emergency department, which grew *F necrophorum*. The remaining blood cultures on postadmission days 3, 4, and 6 were negative. The patient clinically improved while on meropenem and was ultimately discharged with a total of 6 weeks of amoxicillin antibiotic therapy.

3.3. Case 3

A 17-year-old adolescent boy with no significant medical history was admitted with a 1-week history of fevers, chills, night sweats, sore throat, decreased appetite, diffuse body aches, and unintentional weight loss. He further complained of a 3-day history of nausea, vomiting, productive cough, and minor swelling of the left knee. On initial evaluation, standard laboratory tests and blood cultures were obtained, and the patient received cefotaxime, vancomycin, and IV hydration. White blood cell count was 25.2, hemoglobin level 15, hematocrit 45, and platelets 55. Conventional chest radiographs revealed a round opacity of the right lower lung field with cavitation. Subsequent CT imaging of the chest revealed bilateral cavitary nodules, bilateral pulmonary effusions, atelectasis in addition to mediastinal and axillary lymphadenopathy (Fig. 5). The patient was placed in isolation out of concern for tuberculosis, started on Levaquin (Ortho-McNeil Pharmaceutical, Raritan, NJ), and scheduled to undergo an echocardiogram as part of initial evaluation for septic emboli. The patient continued to develop high spiking fevers and began to complain of left-sided neck pain and greater left knee pain. Computed tomography of the neck revealed lymphadenitis and thrombosis of the left internal jugular vein, which was confirmed with ultrasound (Fig. 6). Clinical findings during therapeutic arthrotomy confirmed septic arthritis of the left knee. The initial blood cultures were positive for *F necrophorum*. The patient was started on anticoagulation therapy and received antibiotic therapy for a period of 6 weeks.

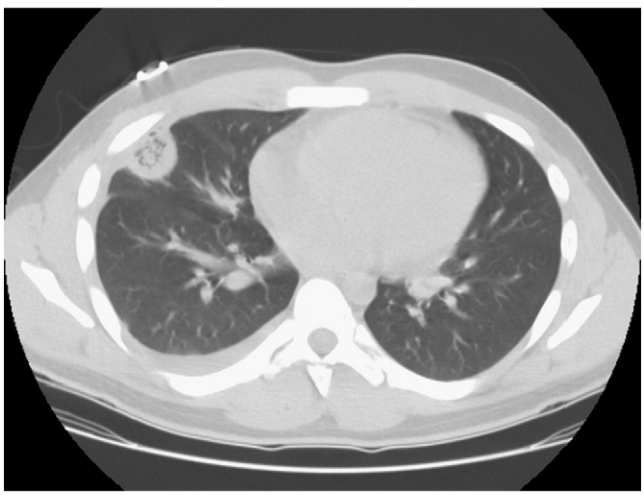

Fig. 5. Axial CT images of the chest with contrast showing bilateral cavitary nodules, bilateral pulmonary effusions, atelectasis, and mediastinal and axillary lymphadenopathy.

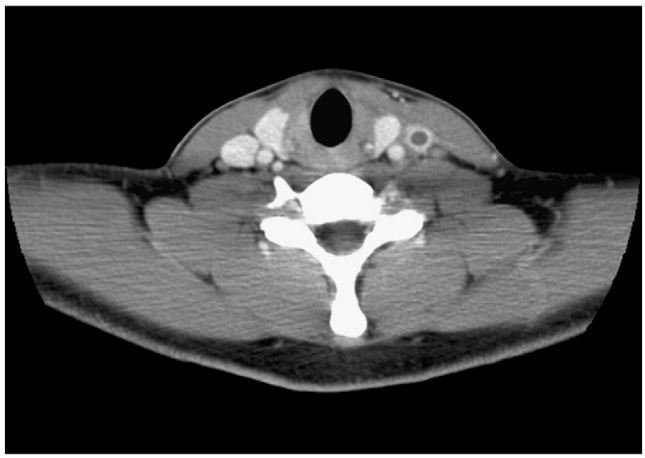

Fig. 6. Axial CT images of the neck with contrast showing lymphadenitis and thrombosis of the left internal jugular vein.

4. Discussion

Lemierre syndrome is a serious complication of progressive head and neck infections. Classically, infection begins in the oropharynx with thrombosis of the tonsillar veins followed by involvement of the parapharyngeal space and the internal jugular vein. Septicemia and pulmonary lesions develop as infection spreads via septic emboli [3]. Although a rare entity in modern times, Lemierre syndrome remains a disease of considerable morbidity and potential mortality because of disease progression and potential diagnostic delays.

Table 1
Causative organisms of Lemierre syndrome

Most common
Fusobacterium necrophorum
Fusobacterium nucleatum
Least common
Bacteroides distasonis
Bacteroides fragilis
Bacteroides gracilis
Bacteroides melaninogenicus
Bacteroides uniformis
Candida sp
Eikenella corrodens
Enterococcus sp
Eubacterium sp
Gemella morbillorum
Lactobacilli
Peptostreptococcus
Proteus mirabilis
Staphylococcus aureus (MRSA)
Staphylococcus epidermidis
Group B *Streptococcus*
Group D *Streptococcus*
Streptococcus oralis

MRSA, methicillin-resistant Staphylococcus aureus.

4.1. Epidemiology

The incidence of Lemierre syndrome has been reported between 0.6 and 2.3 per million, with mortality rates between 4% and 18% [7]. Although the syndrome may affect patients of all ages, more than 70% of cases have been documented in young adults between the ages of 16 and 25 years and show a greater likelihood in males compared to females [7,8]. Most patients are healthy, and as of yet, there has been no link with immunocompromised status. By far, *F necrophorum* has been reported as the most common causative agent with positive cultures in 81.7% of patients according to a study by Chirinos et al [8]. In this same study, 12.8% of patients had sterile cultures and another 5.5% of patients had cultures positive for bacteria other than *F necrophorum* (Table 1, showing a list of all other identified organisms). Polymicrobial infections represent 10% to 30% of cases, with 10.1% of cases involving organisms in combination with *F necrophorum* [5,8].

4.2. Pathogenesis

F necrophorum is a strictly anaerobic, nonmotile, pleomorphic, gram-negative bacillus commonly found in the oral cavity, gastrointestinal tract, and the female genital tract. Current evidence suggests that this organism is responsible for 10% of new cases of pharyngitis [9] and 20% of recurrent cases [10]. Multiple virulence factors including cell wall lipopolysaccharide endotoxin, leucocidin, hemolysin, lipase, hemagglutinin, and a cytoplasmic toxin are produced by *F necrophorum* [11]. Hemolysin lytically destroys erythrocytes, whereas hemagglutinin promotes platelet aggregation [12,13], and it is believed that phospholipase A and lysophospholipase are also key contributors to the hemolytic effects of *F necrophorum* [14]. Leucocidin inhibits leukocyte migration toward the site of infection and protects other facultative organisms from phagocytosis [15,16]. Recently, the 3-gene leukotoxin operon (lktBAC) encoding this virulence factor has been identified in human *F necrophorum*, and functionality of the principal toxin IktA was confirmed [17]. Combined, these factors attenuate the local immune response while promoting an anaerobic environment for bacterial replication [18].

The pathogenesis of *F necrophorum* proceeds through a series of stages. The disease begins in the palatine tonsils and peritonsillar tissue in approximately 87% of cases [8], whereas the remaining 13% of cases involve primary pharyngitis, parotitis, sinusitis, mastoiditis, otitis media, and odontogenic infections [19]. The next stage involves infection of the parapharyngeal space with subsequent invasion of the posterior compartment along the carotid sheath, leading to thrombophlebitis of the internal jugular vein (IJV). Internal jugular vein thrombophlebitis may also develop from extension of thrombophlebitis from the peritonsillar veins, although this appears to be a less common route [8]. In the final stage, spread of infection is observed with direct extension of the organism into the blood system or via septic emboli, leading to a series of metastatic complications (Table 2, showing a list of complications and the rate at which each occurs). Of these complications, involvement of the lungs and joints appear to be the most

Table 2
Complications of septic emboli in Lemierre syndrome

Cardiovascular	Neurologic
Cardiac tamponade	Abscess
Pericarditis	Meningitis
Endocarditis	Sigmoid sinus thrombosis
Carotid artery rupture	Cavernous sinus thrombosis
	Cranial nerve IX-XII palsies
	Horner syndrome
Integument	**Ophthalmic**
Cutaneous pustules	Endophthalmitis
Skin abscess	Subretinal abscess
	Vitreous hemorrhage
Liver	**Pulmonary**
Abscess	Abscess
Liver dysfunction	Pneumatocele
	Pneumothorax
	Pulmonary embolism
	Adult respiratory distress syndrome
Musculoskeletal	**Renal**
Septic arthritis	Abscess
Arthralgia	Glomerulonephritis
Osteomyelitis	Acute renal failure
	Hemolytic uremic syndrome

common, and have an involvement of up to 79.8% and 16.5% of patients, respectively, according to one study [8].

The reemergence of this once forgotten disease is presumed to be the result of discouragement in the use of penicillin therapy for acute tonsillitis as well as improvement in diagnostic and blood culture methods. 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 [12,20,21]. Supporting this hypothesis are several reports of Lemierre disease occurring in conjunction with Epstein-Barr virus pharyngitis and infectious mononucleosis [22,23]. Furthermore, smoking has also been suggested as a factor contributing to *F. necrophorum* infection, as nicotine may enhance toxins from peri-odontopathogens [23].

4.3. Clinical presentation

The progression of clinical symptoms in Lemierre syndrome closely follows the disease course and has been well documented in the literature (Fig. 7; diagram of stages of disease with clinical symptoms of each stage and time course). Clinical findings during the primary infection are dependent on the initial site of infection and most are not specific to the syndrome. Fever is generally present in more than 80% of patients along with abdominal pain, nausea, and vomiting in about 50% of patients by one study [8]. Exudative tonsillitis, oropharyngeal ulcers, cervical lymphadenopathy, and pharyngeal hyperemia are additional common findings at the onset of the disease [24]. Interestingly, it has been observed that symptoms of oropharyngeal infection may clear before progression of the disease, even without prior antibiotic therapy [25,26].

The second stage of infection involving invasion of the lateral pharyngeal space may lead to a variety of additional clinical manifestations depending on the site of invasion. Invasion of the anterior compartment may lead to vascular involvement, whereas invasion of the posterior compartment can lead to cranial nerve X-XII palsies or Horner syndrome [8]. Internal jugular vein thrombophlebitis often manifests as pain and unilateral swelling at the angle of the jaw and along the sternocleidomastoid muscle, and is occasionally associated with trismus. Commonly, the thrombosed IJV itself is rarely palpable [27,28]. Dysphagia has been reported in up to 17.4% of patients in one study [8]. Spasm of the sternocleidomastoid muscle may also occur and paralysis of the trapezius muscle has been reported in one case [29].

During metastatic spread, the septic emboli can produce characteristic clinical findings depending on the site of embolism (Table 2). Embolic disease in the lungs, the most common site of metastatic spread, lead to symptoms resembling an aseptic pulmonary embolism with bilateral nodular infiltrate and occasional cavitation, as in Case 3 above. Associated pleural effusions are common as are lung abscesses and empyema [25,26,28,30]. Pneumothorax and pneumatoceles have also been reported [31]. Finally, frank respiratory failure can occur and has been reported as high as 15.5% according to one study [8].

4.4. Diagnosis

Because of the clinical infrequency of this condition in modern times, the diagnosis of Lemierre syndrome is

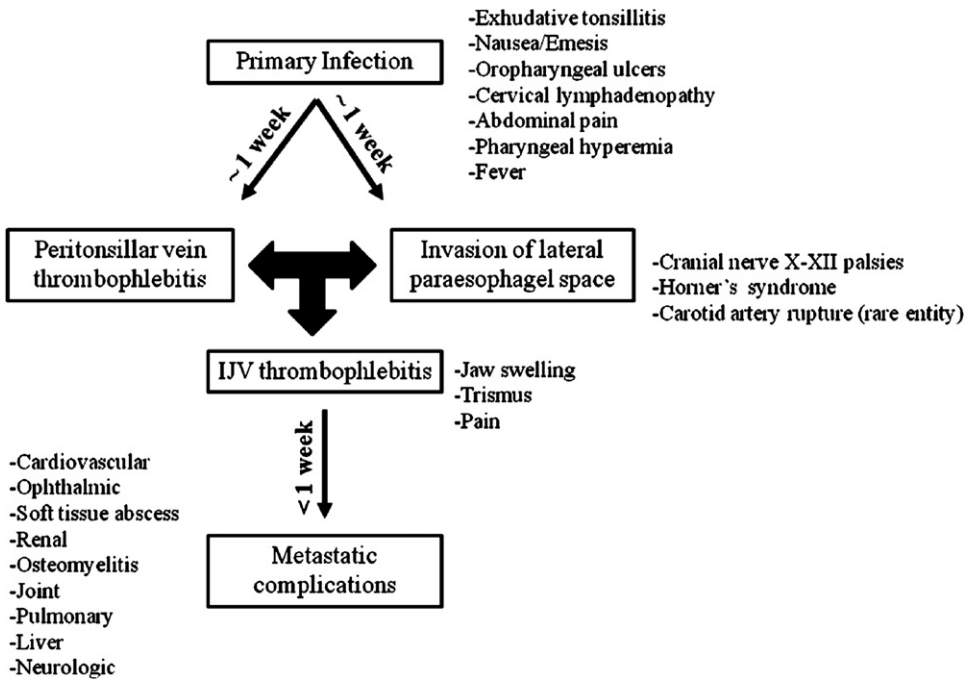

Fig. 7. Clinical progression of Lemierre syndrome.

commonly achieved through laboratory studies rather than clinical observation. The result of this diagnostic delay is that most patients have evidence of metastatic complications by the time of official diagnosis [8]. Today, a blood culture positive for *F necrophorum* is usually the first diagnostic clue, as was the case in approximately 70% of patients in the study by Chirinos et al [8]. Cultures take on the order of 48 hours and appear less sensitive than polymerase chain reaction [7]. Because patients initially present with nonspecific findings of high fever and oropharyngeal infection, a high degree of clinical suspicion is required for accurate diagnosis. In general, clinical suspicion should be aroused when a patient with any head and neck infection develops signs of IJV thrombophlebitis, sepsis, or systemic organ failure from septic emboli.

Contrast-enhanced CT of the neck is the modality of choice for establishing IJV thrombosis [32] and may also be critical in identifying additional head and neck pathologies [21]. Computed tomographic findings typically include distended neck veins, enhanced walls, low attenuation intraluminal filling defects, and soft tissue swelling [33]. Ultrasonography has also been used to identify IJV thrombosis, showing an echogenic region within a dilated vein or a mass consisting of both solid and cystic components [19,26,27]. Its use as primary diagnostic modality is limited however because many authors cite poor imaging quality of the jaw and clavicle region and the possibility of missing a thrombus with low echogenicity as possible downsides of the technique [33]. The use of magnetic resonance angiography, gallium scans, and radionuclide venography has also been reported [19,34,35].

Metastatic infection can be identified through multiple diagnostic modalities. Metastatic infection to the lung is usually diagnosed by a chest radiograph with pulmonary infiltrates, pleural effusion, and occasionally cavitation or empyema. Abdominal ultrasound can identify liver or splenic abscess [36]. Aspiration and culturing of joint fluid are indicated when patients develop arthritis, as is culturing of skin pustules when skin infections are present [22,25].

4.5. Treatment

The combination of early diagnosis with aggressive antimicrobial therapy is essential in the efficient treatment of Lemierre syndrome, although an ideal regimen does not exist today. Traditionally, penicillin has been widely used, but B-lactamase production by some *F necrophorum* limits the use of penicillin as monotherapy [19,33]. Thus, the use of B-lactamase–resistant antibiotic formulations containing clavulanate or sulbactam has been advocated. Some authors recommend combined treatment with high-dose penicillin and metronidazole or monotherapy with clindamycin [21].

The duration of antibiotic treatment is also under debate. A typical course of antibiotics ranges from 3 to 6 weeks, although the duration of treatment can vary from 9 to 128 day as reported in the literature [7]. The response of the infection to treatment is usually slow because bacteria sequestered inside of a septic thrombus in the IJV or inside of a deep abscess in the lung or liver may not be accessible [7]. Although drainage of abscesses is encouraged, there are differing views on the use of anticoagulation [37-39].

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 Lemierre syndrome, but these patients have been shown to display increased factor VIII activity as well as antiphospholipid antibodies. Opponents of anticoagulation argue that the clots associated with Lemierre syndrome generally resolve on their own and outcome is good for the patient, but proponents of anticoagulation support its use for quicker resolution of clots. Given the severity of most presenting patient's symptoms and their associated morbidity, we believe that hastening the resolution of septic emboli is of significant clinical importance and have chosen to anticoagulate patients when thrombosis is observed.

Internal jugular vein ligation or excision was practiced routinely during Lemierre time, but its use today has been limited to those patients with persistent septic embolization after treatment with antibiotics.

5. Conclusion

Lemierre syndrome is a serious complication of head and neck infections, initially involving the oropharyngeal space and ultimately leading to severe systemic compromise. Although a rare clinical entity today, Lemierre syndrome remains a disease of considerable morbidity and potential mortality. Timely recognition of disease progression is crucial in preventing severe systemic manifestations. To avoid diagnostic delays we advocate the early use of CT/US imagining and polymerase chain reaction–based serological screens. Empirical broad-spectrum antibiotic treatment should not be delayed and should include a third generation cephalosporin. Lastly, we recommend the use of anticoagulation in individuals with confirmed jugular thromboses to expedite recovery.

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