Eponyms in medicine revisited

Lemierre's syndrome (necrobacillosis)

Rafael Golpe, Belén Marín, Miguel Alonso

Summary

Lemierre's syndrome or postanginal septicæmia (necrobacillosis) is caused by an acute oropharyngeal infection with secondary septic thrombophlebitis of the internal jugular vein and frequent metastatic infections. *Fusobacterium necrophorum* is the most common pathogen isolated from the patients. The interval between the oropharyngeal infection and the onset of the septicæmia is usually short. The most common sites of septic embolisms are the lungs and joints, and other locations can be affected. A high degree of clinical suspicion is needed to diagnose the syndrome. Computed tomography of the neck with contrast is the most useful study to detect internal jugular vein thrombosis. Treatment includes intravenous antibiotic therapy and drainage of septic foci. The role of anticoagulation is controversial. Ligation or excision of the internal jugular vein may be needed in some cases.

Keywords: Lemierre's syndrome; *Fusobacterium necrophorum*; necrobacillosis; septicæmia; oropharynx

Characterisation of Lemierre's syndrome

Acute oropharyngeal infection followed by septic thrombophlebitis of the IJV and metastatic infections, most frequently involving the lungs

Box 1

Respiratory Section, University Hospital Marqués de Valdecilla, Santander, Spain

R Golpe
B Marín
M Alonso

Correspondence to Rafael Golpe, General Pardiñas 6–4°, 15701 Santiago de Compostela, Spain

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Postanginal septicæmia (also called necrobacillosis and Lemierre's syndrome) is caused by an acute oropharyngeal infection with secondary septic thrombophlebitis of the internal jugular vein (IJV), frequently complicated by metastatic infections. It was first reported by Courmont and Cade in 1900,¹ although the syndrome was best characterised by Lemierre in 1936 from a review of 20 cases.² In the pre-antibiotic era it was not uncommon and it had a fulminant, usually fatal, evolution in 7 to 15 days. Since the introduction of antibiotics and their widespread use for the treatment of throat infections, there has been a substantial decrease in the incidence of postanginal septicæmia. Because of this, the syndrome is frequently overlooked when it appears today.³ However, the presentation is so characteristic that clinical diagnosis is possible in most cases, and with appropriate therapy a cure is to be expected in the overwhelming majority of patients, so that it is essential for the clinician to be aware of this not-so-rare syndrome.

Aetiology

Fusobacterium species are normal inhabitants of the oral cavity, the female genital tract, and the gastrointestinal tract. *F. nucleatum* and *F. necrophorum* are the species most frequently isolated from clinical specimens.⁴ *F. necrophorum*, which is the more virulent of the two, is the most common pathogen isolated in patients with Lemierre's syndrome. This is a strictly anaerobic, non-motile, Gram-negative bacillus with a somewhat bizarre morphological appearance on Gram-stained smears. It can be difficult to identify and may be mistaken for *Bacteroides*.⁵ It has received numerous names, including *Bacillus funduliformis*, *Bacteroides funduliformis*, *Sphaerophorus necrophorus*, and *Bacteroides necrophorus*.³ *F. necrophorum* has an unusual ability to invade as a primary pathogen in previously healthy people, unlike other anaerobic bacteria. This feature is related to its toxins, which are distinct from those of other anaerobes.^{5–7} *Fusobacterium* strains have a lipopolysaccharide endotoxin similar to nonanaerobic Gram-negative bacilli, with strong biologic activity. *F. necrophorum* also produces a leukocidin and haemolysin, which probably augment its virulent properties.^{3, 8, 9} Aggregation of platelets by broth cultures and washed cells of *F. necrophorum* has been observed, and is also thought to be related to the virulence of the organism.³

Other causative organisms, such as *Streptococcus* sp, *Bacteroides* sp, *Peptostreptococcus* sp, and *Eikenella corrodens*, are found occasionally in Lemierre's syndrome.^{3, 6, 10} In some cases, more than one pathogen is isolated from the patient.^{3, 4, 11}

Pathogenesis

The palatine tonsils and peritonsillar tissue are the primary source of infection in the majority of cases, although pharyngitis, parotitis, otitis media, sinusitis, odontogenic infection and mastoiditis have been described as causes of the syndrome.^{3, 6} Infection of the lateral pharyngeal (parapharyngeal) space may result from these sources. This space is divided by the styloid process into an anterior (muscular) compartment and a posterior (neurovascular) compartment. The carotid sheath, which includes the carotid artery and the IJV, as well as the vagus nerve and lymph nodes, is located in the posterior compartment.³ Infection of this compartment can cause complications such as thrombophlebitis of the IJV and severe sepsis with frequent metastatic infections. This complication can also result from extension of thrombophlebitis in the peritonsillar veins into the IJV.³

The reason why *F. necrophorum* becomes invasive is unknown. Several cases of Lemierre's syndrome preceded by infectious mononucleosis have been reported,^{11, 12} so that some authors have suggested the possible role of primary viral throat infection as a risk factor for the syndrome.³ Enhancement of toxins from several peri-odontopathogens by nicotine has been suggested by one study,¹³ suggesting that smoking might be another factor which increases the possibility of developing aggressive oropharyngeal infection by anaerobes.

Aetiology

- *Fusobacterium necrophorum*, an anaerobic, non-motile, Gram-negative bacillus, is the most common pathogen
- unlike other anaerobes, *F. necrophorum* is frequently the sole pathogen; this feature is related to its toxins
- other aetiological organisms are occasionally found

Box 2

Pathogenesis

- infection of the posterior (vascular) compartment of the lateral pharyngeal (parapharyngeal) space is of primary importance
- the reason why *F. necrophorum* becomes invasive is unknown, although primary viral throat infection might play a role
- parapharyngeal space infection leads to thrombophlebitis of the IJV, which is located in this compartment
- metastatic infections develop from this source

Box 3

Clinical presentation

- the interval between oropharyngeal infection and septicaemia is usually ≤ 1 week.
- oropharyngeal symptoms may have improved by the time septicaemia develops
- parapharyngeal space infection and IJV thrombosis produce local signs and symptoms, but these can be subtle
- lung involvement is common, including pulmonary infiltrates, pleural effusion, lung abscess, empyema, pneumatoceles and pneumothorax
- other sites of metastatic infection include joints, bone, liver, spleen, skin, soft tissues, kidney and meninges
- hyperbilirubinaemia and elevation of liver enzyme levels are common
- morbidity is high, but deaths are uncommon nowadays with appropriate therapy

Box 4

Clinical presentation

As previously mentioned, the oropharynx is the primary site of infection in most cases. Exudative tonsillitis is frequently present, but other findings, from ulcers to simple hyperaemia of the pharynx may be noted. The interval between the oropharyngeal infection and the onset of the septicaemia is usually a week or less.³ However, signs and symptoms related to oropharyngeal infection may have cleared by the time IJV thrombosis or metastatic infection develop, even without prior antibiotic therapy.¹⁴⁻¹⁶ Therefore, it is easy to misdiagnose the syndrome as infectious endocarditis in a patient who presents with evidence of septic emboli.¹⁶ This mistake has obvious therapeutic implications regarding initial empiric antibiotic therapy.¹⁶ Postanginal septicaemia with renal complications has also been misdiagnosed as post-streptococcal glomerulonephritis.¹⁷

When lateral pharyngeal space infection and thrombophlebitis of the IJV develop, signs and symptoms include pain and swelling or induration at the angle of the jaw and along the sternocleidomastoid muscle, sometimes with associated trismus.^{8, 15} The thrombosed jugular vein is rarely palpable.¹⁵ It must be remembered that local findings can be subtle or absent,¹⁶ especially if the infection affects selectively the posterior compartment of the lateral pharyngeal space.³

As a consequence of the continuous bacteraemia generated by the endovascular infection, septic embolisms develop. The most common site of embolic disease is the lungs.^{3, 6} The symptoms resemble aseptic pulmonary embolism. The chest X-rays show bilateral, usually nodular, infiltrates that sometimes cavitate. Associated pleural effusion is common,¹⁴⁻¹⁶ and may precede the appearance of pulmonary infiltrates.¹¹ Empyema and lung abscess are relatively frequent,^{16, 18, 19} and both pneumatoceles and pneumothorax have been described.²⁰

Septic arthritis and osteomyelitis are also seen, although less frequently now than in the pre-antibiotic era.^{3, 21} Hepatic and splenic abscesses have been reported, but they are rare.^{7, 22} However, splenomegaly and hepatomegaly are common.^{7, 23} Mild hyperbilirubinaemia with slight elevation of liver enzyme levels is found in many cases. Some authors have hypothesized that toxicity to the hepatobiliary system due to circulating bacterial endotoxins is the cause.^{4, 6} Histopathologic examination of the liver in these cases usually shows intrahepatic cholestasis with little or no hepatocyte necrosis. Kupffer cell hyperplasia, nonspecific hepatitis, increase in lymphocytes in portal areas and fatty vacuolization have been described less commonly.^{3, 20} These changes are usually asymptomatic, but jaundice sometimes occurs.^{3, 5, 20}

Some patients have soft tissue abscesses and cutaneous pustular lesions.^{3, 11, 20, 23} Pyomyositis has also been described as a complication of *F. necrophorum* sepsis.²⁴ Transient haematuria and elevation in serum creatinine have been reported,³ and meningitis has been seen, although rarely.^{3, 12} A case report described two children with pancytopenia associated with necrobacillosis; bone marrow infarcts were found in one of these patients.²⁵

The outcome of the syndrome after appropriate therapy has been instituted is favourable in most patients, although adult respiratory distress syndrome has been reported,¹⁹ and fatal cases are seen even in the postantibiotic era.^{3, 4} The morbidity is high and hospital stays are frequently long.³

Diagnosis

A high degree of clinical suspicion is needed if symptoms from oropharyngeal infection or from any of the described sources of infection are accompanied or followed by data suggestive of IJV thrombophlebitis, sepsis or septic emboli. Persistent fever may be the only evidence of the syndrome, particularly during the earlier phases. As previously mentioned, oropharynx examination findings may not be diagnostic,¹⁴ and the syndrome is frequently not suspected until microbiology results are available.

The clinical suspicion of IJV thrombophlebitis must be objectively confirmed. Computed tomography (CT) of the neck with contrast is the most useful investigation. It can reveal distended veins with enhancing walls, low attenuation intraluminal filling defects, and swelling of the adjacent soft tissues.⁶ It assists in localising abscesses that require drainage.⁸ Ultrasonography is less expensive and less invasive than CT and has been successfully used to demonstrate IJV thrombosis.¹⁴ It will reveal an echogenic region within a dilated jugular vein, or a complex mass of solid and cystic components.⁸ However, it provides poor imaging beneath the clavicle and under the mandible, and can miss a fresh thrombus with low echogenicity, so some authors suggest using it only as an adjunct, and for following the evolution of the thrombus.⁶ Magnetic resonance angiography has also proved useful for diagnosing IJV thrombosis.⁸

Diagnosis

- a high degree of clinical suspicion is needed
- IJV thrombosis can be confirmed by neck CT with contrast, ultrasonography, MR angiography, conventional venography (rarely used today), gallium scan and radionuclide venography with Tc 99m-labelled red blood cells
- X-rays and ultrasound studies usually suffice to detect metastatic infection
- isolation of the causative organism can be made from blood cultures or from specimens obtained from sites of metastatic infection

Box 5

Treatment

- intravenous β -lactamase-resistant antibiotics directed at anaerobes is the mainstay of therapy
- anticoagulation therapy is controversial; it may be useful if septic emboli persist despite antibiotic therapy or if thrombosis propagates to the cavernous sinus
- excision or ligation of the IJV may be needed if emboli are not controlled with medical treatment

Box 6

Conventional retrograde venography is less used today because of its invasiveness compared with other imaging methods. However, some authors believe that it can be useful to assess precisely the extension of the thrombosis when jugular vein ligation, discussed below, is considered.¹⁵ Other techniques that can lead to the diagnosis of IJV thrombosis include gallium scan¹⁰ and radionuclide venography with Tc-99m-labelled red blood cells.²⁶

Simple imaging studies usually allow the diagnosis of metastatic infections. Chest X-ray findings in patients with pulmonary septic emboli are mentioned above. High-resolution CT can sometimes provide additional useful information.²⁷ Abdominal ultrasonography is indicated when liver or splenic abscesses are suspected.^{7, 33}

The causative organism can be isolated from blood cultures or from other specimens processed anaerobically, if obtained before initiating therapy. When arthritis is present, fluid from the involved joints must be cultured.¹⁶ Cultures of skin pustules and pus from liver abscesses can also yield positive results,^{7, 11} as can culture of pus obtained from empyemas.^{5, 16, 18} *F. necrophorum* has also been isolated from samples obtained through bronchoscopy in a patient with septic pulmonary emboli in whom blood cultures were negative, so that this procedure should be considered in the presence of pulmonary infiltrates.²⁸

Treatment

The mainstay of treatment is intravenous antibiotics directed at anaerobic microbes. Prolonged antibiotic therapy seems to be necessary for eradication of the infection, probably because of its endovascular nature.⁸ *F. necrophorum* has been traditionally susceptible to penicillin, clindamycin, metronidazole and chloramphenicol, but activity of the cephalosporins, erythromycin and tetracyclines have been variable.^{4, 6} It must be noted that some treatment failures with penicillin have been reported.^{16, 29} β -Lactamase production by some *F. necrophorum* might account for this observation,^{6, 30} so that β -lactamase-resistant antibiotics with anaerobic activity (ticarcillin-clavulanate, ampicillin-sulbactam, etc.) are recommended today.^{6, 29}

Sinave *et al* note that, because the decrease of necrobacillosis incidence in the postantibiotic era is probably a consequence of the widespread use of antibiotics for oropharyngeal infection, it would be tempting to recommend treatment with oral antimicrobial agents in all cases of non- β -haemolytic group A streptococcal pharyngitis. However, this is not considered cost-effective, because of the probable low incidence of anaerobic infection in relation to other aetiologies of acute pharyngitis.³

During antibiotic therapy, close observation for signs of continued sepsis, propagation of thrombus or metastatic infection is essential, and purulent collections must be drained.

The role of anticoagulant therapy in Lemierre's syndrome is somewhat controversial, because the outcome of most patients is good without it. One study suggested that the addition of heparin was associated with a quicker resolution of septic pelvic thrombophlebitis, and this observation might support the use of anticoagulation in Lemierre's syndrome.³¹ However, there are no controlled studies that assess its value in septic thrombophlebitis of the IJV. Some authors recommend anticoagulation when septic emboli persist despite antibiotic therapy,²⁰ and others reserve it for patients with clinical evidence of IJV thrombosis propagating retrogradely to the cavernous sinus.⁶

Finally, in patients with uncontrolled sepsis and repeated septic emboli despite appropriate medical therapy, surgical ligation or excision of the IJV should be performed,⁶ although this treatment is rarely needed today.

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