The ‘Forgotten Disease’ (or the Never Known)

KA Sudarshana Murthy¹, T Thippeswamy², HS Kiran³, CR Venkatesh⁴, S Harsha⁵, T Shivaram Shetty⁶, Akash Shukla⁷

Abstract
Lemierre’s syndrome is an acute oropharyngeal infection with secondary septic thrombophlebitis of the internal jugular vein and frequent metastatic infections. Despite its rarity, it is important to have a high degree of clinical suspicion to recognise it early. A history of sore throat followed by metastatic infections and abscesses should alert the clinician to the possibility of this unusual infection. We present a case of Lemierre’s syndrome presenting with meningitis in a previously healthy young adult along with a review of the pathophysiology of necrobacillosis and its diagnosis, diagnostic difficulty and treatment.

Introduction

Also described variously as necrobacillosis, postanginal septicaemia and ‘the forgotten disease’,¹ Lemierre’s syndrome is characterised by frequent metastatic infections, disseminated abscesses and thrombophlebitis of the internal jugular vein after infection of the oropharynx. It is classically anaerobic in origin and Fusobacterium necrophorum is the most common pathogen. The organisms most frequently involved in postanginal sepsis are Fusobacterium species and anaerobic Streptococci, and less commonly isolated are alpha-haemolytic and group A beta-haemolytic Streptococci, S. pneumoniae, S. aureus, and E. corrodens.

Case History

A 25 year-old previously healthy male from a malaria endemic rural background presented to the Emergency room with complaints of fever, rigors, headache, neck pain and projectile vomiting for the past 15 days. He was admitted and treated elsewhere with antibiotics and antimalarials intravenously.

Review of symptoms revealed a 10 day history of sore throat, prior to admission. He denied any significant medical problem in the past.

At presentation, the patient’s vital signs included a temperature of 100°F, a regular pulse of 100 beats per minute, a respiratory rate of 20 breaths per minute, and a supine blood pressure of 106/70 mmHg with no postural drop. He was pale and had icterus. Oral examination demonstrated erythema of the posterior pharyngeal mucosa and the faucial pillars. Right upper posterior cervical lymph nodes were enlarged and slightly tender. The lungs were clear on auscultation. Cardiac examination revealed tachycardia, but failed to demonstrate murmurs, rubs, or gallops. Abdominal examination revealed a splenomegaly of 4 cm below the left costal margin and tenderness in the right Hypochondrium. Nervous system examination revealed a conscious, but irritable patient with no motor weakness. Neck stiffness was present and Kernig’s and Brudzinski signs were positive. Bilaterally, plantars showed a flexor response. Fundus examination revealed changes consistent with bilateral early papilloedema.

Laboratory data revealed the following: Haemoglobin 10.9 g/dl, haematocrit 43.2%; leucocyte count 8600/mm³ (86% granulocytes, 14% lymphocytes); platelet count 4.3
L/mm³; Erythrocyte Sedimentation Rate of 14 mm, serum electrolytes- sodium 136 mmol/l, potassium 3.9 mmol/l; blood urea 58 mg/dl; creatinine, 1.1 mg/dl; total bilirubin 4.4 mg/dl with 2.2 mg/dl of direct bilirubin, Total Protein 7.0 gm/dl, Albumin 4.0 gm/dl, A/G ratio 1.3, AST 38 IU and ALT 27 IU, S. Alkaline Phosphatase 43 IU, Gamma Glutamyl Transferase 70 IU. Paired blood samples failed to grow organisms on culture. QBC for malarial parasites was negative for 3 samples. Serological tests for Dengue, Leptospirosis, Paul-Bunnel test, Weil-Felix test, HBsAg and HIV by ELISA were negative. Electrocardiogram showed sinus tachycardia. Chest radiograph performed on admission did not demonstrate any radiological abnormality. Ultrasound Abdomen revealed splenomegaly and mild hepatomegaly. CT head being normal, CSF analysis showed a hazy fluid with an elevated protein of 118 mg/dl with a reduced glucose of 29 mg/dl, a cell count of 48 cells with lymphocyte predominance of 72%, neutrophils 15% and 13% mononuclear cells. CSF failed to demonstrate positivity for gram’s stain, acid fast organisms, capspulated organisms, VDRL and malignant cells.

A presumptive diagnosis of viral meningitis vs complicated malaria vs tubercular meningitis was considered and the patient was treated with IV antibiotics (Ceftriaxone), anti malarials and anti oedema measures with mannitol, anti pyretics, maintenance of adequate hydration with IV fluids and other symptomatic and supportive treatment.

The patient continued to run spikes of fever and was toxic. By the fourth day, the patient complained of throbbing pain in the right angle of the jaw and on the right side of the neck. Otorhinolaryngologist consultation was arranged, who opined the patient having B/L suppurative otitis media.

Persistent nuchal pain prompted a CECT of the neck, which demonstrated a para pharyngeal abscess with partial obliteration of the right Internal jugular vein. A throat swab culture for both aerobes and anaerobes failed to grow pathogens. ANA done at this juncture was negative. Gram negative and anaerobic coverage with broad spectrum antibiotics, anticoagulation with low molecular weight Heparin was started, followed by a dramatic improvement in the patient’s symptomatology within 48 hours. Though CSF picture favoured chronic meningitis, it was concluded that it could possibly point towards an inadequately treated acute bacterial meningitis. The patient was discharged in two weeks time after long term intravenous antibiotics covering both aerobes and anaerobes. The follow up visits were uneventful and the patient made a satisfactory recovery over the next month. The patient is on regular follow up since 4 months and is doing well.

Discussion

Courmont and Cade in 1900 first reported a potentially fatal septicaemia which they described as post anginal septicaemia. But, it was not until 1936, that the syndrome was best characterised by Lemierre Andre, from a review of 20 cases as a lethal oropharyngeal infection resulting in internal jugular vein thrombophlebitis, bacteraemia and septic embolisation which, unlike other gram negative septicaemias affecting usually the elderly and the debilitated, typically affected previously healthy adolescents, with a male predominance. The illness described by Lemierre was rapidly fatal (within 7–15 days) in 18 of the 20 cases he reported. Lemierre found the clinical picture so characteristic as to constitute “a syndrome whose diagnosis would be almost impossible to mistake and permits a diagnosis before bacteriological examination, including blood culture, has provided conclusive proof.”

In the post Antibiotic era, widespread use of antibiotics for the treatment of throat infections has seen a substantial decrease in the incidence of postanginal septicaemia. Hence it is rarely being picked up, of late. The diagnosis of Lemierre’s syndrome can be made only if the clinician is aware of the condition.

There is a notable decline of reported cases over the last few years. Alston reported 269 cases in 1955, Gunn 148 in 1956, while Sinave found only 38 reported cases between 1974 and 1978. Studies of the incidence rates for Lemierre’s syndrome have shown figures between 0.6 and 2.3 per million population and more commonly in males. In 1998, Hagelskjæer et al reported an incidence of 0.8 cases per million per year for Lemierre’s syndrome following a retrospective review of medical and microbiological reports of the general population from 17 centres in Denmark over a 6-year period. Although most patients reported are healthy teenagers or young adults, without apparent medical history, infants and aged patients with or without underlying chronic disease are not the exception.

The primary sources of infection include the palatine tonsils (87.1%), followed by odontogenic infection and lastly undetermined. The extrapharyngeal primary sites of infection include the middle ear, the female urogenital tract and the gastrointestinal tract.

The criteria mentioned by Sinave et al. for “Classical Lemierre’s syndrome” are as follows:

i. Primary infection in the oropharynx
ii. Septicaemia documented by at least one positive blood culture
iii. Clinical or radiographic evidence of IJV thrombosis
iv. At least one metastatic focus.

However, nowadays because of the early use of antibiotics, blood cultures may be more often negative.

*F. necrophorum* (previously known as *Bacillus funduliformis*, *Bacillus necroformis*, *Bacteroides funduliformis*, *Necrobacterium fundiliforme*, and *Sphaerophorus necrophorus*) is the organism most commonly isolated in cases of postanginal sepsis. It is a strictly anaerobic, nonmotile, non-spore-forming, gram-negative bacillus. *Bacteroides* species and other *Fusobacterium* species, including *F. naviforme* and *F. nucleatum*, are less commonly associated with postanginal sepsis. As an anaerobe, it has the unusual capacity to invade as a primary pathogen. It possesses a lipopolysaccharide endotoxin and various exotoxins including leucocidin, haemolysin, lipase, and a cytoplasmic toxin. 3

Typically, the syndrome of postanginal sepsis starts with an episode of pharyngitis or tonsillitis, bacterial or viral, which impairs the oropharyngeal mucosal defense system. This is followed by a tonsillar or a peritonsillar abscess in turn followed by septic thrombophlebitis of the tonsillar and peritonsillar veins. The infection then invades the lateral pharyngeal space due to direct extension, or by lymphatic or venous dissemination followed by sepsis with high fever and rigors, followed by “cord signs” i.e, swelling and tenderness along the sternocleidomastoid muscle representing internal jugular vein thrombophlebitis and metastatic abscesses develop 4 to 12 days after the intraoral infection.

After invasion of the IJV occurs, symptoms may be related to the local involvement of the parapharyngeal space area or metastatic complications. Clinical features of the invasion of this compartment result from the compromise of the vital structures in the parapharyngeal space. A tender, swollen neck, dysphagia and trismus may also be present. Later on, complications of bacteraemia and metastatic infection become evident. The first pass filters, the lungs are the most commonly involved in Lemierre’s syndrome. Septic infarcts giving rise to multiple abscesses can present with dyspnoea, intense thoracic pain, and sometimes, haemoptysis. Chest roentgenograph shows scattered nodular infiltrates and small pleural effusions. Cavitation, empyema, pneumatoceles, pneumothorax, respiratory failure and pulmonary embolism have also been documented.

The primary site of infection determines the clinical presentation. Fever occurs in most but not all cases. In most patients, sore throat and pharyngeal inflammation are the primary findings. Abdominal pain, nausea and vomiting have also been reported. By the time sepsis occurs, the oropharynx may have a normal appearance. Apart from the common metastatic infections of the lungs, osteomyelitis, septic arthritis, disseminated intravascular coagulopathy, meningitis, carotid thrombosis, mediastinal infection with pericardial tamponade, and liver abscesses are other dreaded complications. Ruptures of the carotid artery, Horner syndrome, and paralysis of the trapezius muscle have been reported.

Once this condition is suspected, the internal
jugular veins must be examined for evidence of thrombophlebitis either by ultrasound, magnetic resonance imaging, or CT scan.

CECT Scan of the neck can reveal distended veins with enhancing walls, low attenuation intraluminal filling defects, and swelling of the adjacent soft tissues (Figures 1 and 2).

Isolation of the organism is by culture from blood or other specimens processed anaerobically, which is to be obtained before initiating therapy. Organisms have been cultured in metastatic infections from pus from the abscess site, pus from liver abscesses, synovial fluid from the involved suppurated joints, cerebro spinal fluid in meningitis and from broncho alveolar lavage fluid in lung infections. Throat swab is usually negative in patients with Lemierre’s syndrome.

Principles of treatment of this condition consists of aggressive antibiotic therapy, supportive care and adequate fluid resuscitation. Intravenous broad spectrum beta-lactamase-resistant antibiotics with anaerobic coverage with clindamycin or metronidazole is the accepted choice. Monotherapy with anaerobic coverage alone is not advisable. There are no recommended figures for the duration of antibiotic therapy but treatment is usually given for a period of 3 to 6 weeks. Surgical drainage of the purulent collections should be initiated, if an abscess develops.

The role of anticoagulation therapy is controversial. Conflicting reports have been published on this issue. Although some authors recommend its use as an adjunct to antibiotic therapy, regarding the potential for more rapid resolution of thrombophlebitis and bacteraemia, others have questioned the benefit of anticoagulants, regarding the risks of haemorrhage and extension of infection. It may be useful if septic emboli persist despite antibiotic therapy or when there is evidence of retrograde thrombosis propagating to the cavernous sinus. Rarely, excision or ligation of the IJV, which was the treatment of choice in the pre-antibiotic era may be needed if emboli are not controlled with medical treatment.

Conclusion

The authors have presented a rare case of Lemierre’s syndrome. Although no organism could be isolated on blood and throat swab cultures, this may be explained by the initiation of high dose antibiotics in the community before presentation. Though lung disease was not evident, a neuroinfection by probable septic emboli is likely. The CSF picture seen in the above case favours an inadequately treated acute meningitis which showed features of chronicity.

There are hardly any reports of Lemierre’s syndrome in Indian literature. The authors feel, this case would serve to familiarise several physicians to look for this extremely uncommon, unfamiliar, potentially life threatening clinical entity as a rare serious complication to which pharyngitis or tonsillitis can progress and the key to diagnose lies in a high index of ‘Clinical suspicion’.

Acknowledgements

The authors thank the Department of Radiology and Imaging, JSS Medical College Hospital, JSS University, for their cooperation.

References