CASE REPORT

Lemierre's syndrome: a pain in the neck with far-reaching consequences

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SUMMARY

Lemierre's syndrome is a potentially life-threatening consequence of oropharyngeal and ear infections and often results in critical care admission and even intubation. Due to the multisystem manifestation, multiple teams may initially be involved in the care, some of which may be unfamiliar with the features and usual clinical course. This report describes a case in a 36-year-old woman with the classic features of internal jugular vein thrombosis and septic emboli to the lungs secondary to an oropharyngeal infection. Treatment comprised antibiotic therapy, anticoagulation and fluid resuscitation, and was carried out in a high dependency unit setting. At follow-up 3 months after discharge, the patient was well with no residual symptoms off all treatment. During the events of this case, it became apparent that while ear, nose and throat and infectious diseases team members were relatively familiar with the condition, other departments including the critical care team were less so.

BACKGROUND

Andre Lemierre, a French professor of bacteriology, published an article in *The Lancet* in March 1936 discussing anaerobic septicaemia and the subsequent phenomenon of septic emboli. In his original article, he discussed 20 cases predominantly caused by *Bacteroides funduliforme*, a subspecies of *Fusobacterium necrophorum*. Lemierre described a constellation of symptoms involving spread of thrombophlebitis from a tonsillitis or an untreated peritonsillar abscess to the tonsillar and peritonsillar veins and subsequently to the internal jugular vein (IJV). He also spoke of 'metastatic abscesses' resulting in secondary foci of infection, most commonly identified in the lungs.¹ Although Lemierre's syndrome represents a dramatic pathological process and can often involve multiple systems, mortality is relatively low compared with other disseminated septic states. Case series report between 0% and 18% mortality²; a marked improvement compared with Lemierre's original 90%.¹ Much of this improvement in survival can be attributed to the discovery and widespread use of antibiotics. For several decades following Lemierre's publication, the disease was seldom encountered and even came to be known as a 'forgotten disease'. Over the last few decades, reports of the condition have significantly increased; a phenomenon attributed to more restrictive antibiotic prescribing practices for oropharyngeal infections in the face of growing antimicrobial resistance.^{3,4}

Although Lemierre first described *F. necrophorum* ssp *funduliforme*, it has since become apparent that there is a second subspecies, *F. necrophorum* ssp *necrophorum*, which has only been isolated in animal hosts, and *funduliforme* is accepted as the disease-causing subspecies in humans.⁵ *F. necrophorum* is by no means guaranteed to cause severe disseminated sepsis. It has been identified as a cause of recurrent sore throat, quinsy, tonsillitis and pharyngitis.⁵⁻⁷ As yet the factors that result in disseminated disease are poorly understood. A 2005 paper comparing isolates from sufferers of recurrent sore throat with isolates from individuals with Lemierre's syndrome found no significant difference.⁵ Lemierre included in his original definition other primary sources of infection resulting in septic emboli and infective metastases including otitis media, mastoiditis, appendicitis and infections of the genitourinary system.¹ It is important to note that despite *F. necrophorum* being isolated in several different conditions arising in the oropharynx, it has not been conclusively proved to be a commensal.^{5,7} In vitro studies have demonstrated that preinfection by other bacteria provides an environment for superinfection with *F. necrophorum* colonies that might otherwise be incapable of invasion in normal tissues,⁸ and this may in part explain why *F. necrophorum* is often isolated in conjunction with multiple other organisms.

Treatment and outcomes for Lemierre's syndrome have improved dramatically since its original description. This case highlights, however, that unless clinicians are aware of the possibility, it may initially be missed, allowing several days to elapse before the diagnosis is made and treatment commenced.

CASE PRESENTATION

A 36-year-old female patient presented to the accident and emergency department with a 1-week history of progressively worsening odynophagia and poor oral intake associated with fever, general malaise and reduced urine output. Additionally, she also had myalgia, vomiting, right-sided abdominal and flank pain with some involvement of the hip.

Initial examination in the emergency department (ED) revealed enlarged erythematous tonsils with some pus points, a right submandibular swelling and tender lymphadenopathy. At this point, the patient was hypotensive with a blood pressure of 76/60 mm Hg, tachycardic with a heart rate of 135 beats per minute and displayed clinical signs of shock. Rapid crystalloid infusion was commenced,

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but despite greater than 20 mL/kg, she remained hypotensive. Specialist consultations were sought from ear, nose and throat (ENT) and general surgery. In view of persistent hypotension, the critical care team were called resulting in transfer to the high dependency unit (HDU) for further haemodynamic support. ENT review corroborated the initial findings in the ED, documenting erythematous tonsils with exudate and a large tender level II lymph node on the right. Flexible nasendoscopy did not show any additional abnormalities, and neck movements were normal.

INVESTIGATIONS

Initial bloods: significant thrombocytopenia ($28 \times 10^9/L$) but normal clotting profile and haemoglobin (Hb; $>10 \text{ g/dL}$). Acute kidney injury (creatinine $123 \mu\text{mol/L}$, urea 12.1 mmol/L). Normal white cell count but elevated C reactive protein (330 mg/L).

Admission chest X-ray: left lower zone changes consistent with infection and probable right lower zone atelectasis.

Repeat bloods: improving renal function (urea 9.5 mmol/L , creatinine $88 \mu\text{mol/L}$), Hb dropped to 9.2 g/dL with worsening thrombocytopenia ($15 \times 10^9/L$). At this point, serum tests also ruled out pregnancy and pancreatitis.

Day 2 bloods: improving platelet count ($51 \times 10^9/L$) but rising white cells ($13.8 \times 10^9/L$).

Ultrasound: performed in view of abdominal pain showed thick-walled gall bladder but no stones and a normal common bile duct.

Day 3 bloods: renal function normalised. Hb stable (9.2 g/dL), ongoing thrombocytopenia ($33 \times 10^9/L$). Negative glandular fever, Epstein-Barr virus (EBV), human immunodeficiency virus (HIV) and cytomegalovirus (CMV) tests.

Blood culture results on day 3: *F. necrophorum*.

CT neck, thorax and abdomen on day 3: bilateral pleural effusions as well as a filling defect in the right jugular vein and multiple cervical nodes less than a centimetre, the largest at level II on the right. Incidental finding of acalculous cholecystitis.

DIFFERENTIAL DIAGNOSIS

The patient was originally referred by ED as a possible quinsy. This was modified to acute tonsillitis after review by ENT.

At the time of admission to the HDU, the diagnoses were tonsillitis, left lower zone pneumonia (based on chest X-ray findings) and acute kidney injury (AKI).

Senior review by the critical care team first suggested the possibility of disseminated sepsis, potentially with disseminated intravascular coagulation and also raised the possibility of an autoimmune or vasculitic process. There was also the suggestion of EBV or CMV infection until laboratory testing refuted this.

General surgical review added the possibility of cholecystitis with possible biliary sepsis.

It was not until blood cultures isolated *F. necrophorum* that the unifying diagnosis of Lemierre's syndrome was reached.

TREATMENT

Initial treatment was with intravenous piperacillin and tazobactam in conjunction with fluid resuscitation and a platelet transfusion under close monitoring on HDU. When culture results became available, therapy was switched to benzylpenicillin and metronidazole. Intravenous heparin was started for anticoagulation under a specific regimen whereby therapy would be stopped and platelet transfusion started if the platelet count fell below $50 \times 10^9/L$. After 2 days of intravenous heparin, the patient was switched to 1.5 mg/kg subcutaneous enoxaparin.

Intravenous antibiotics were switched to oral amoxicillin and metronidazole after 2 weeks, and the patient was discharged after 23 days in hospital to complete a total of 4 weeks' oral antibiotic therapy and 3 months of oral anticoagulation with rivaroxaban.

OUTCOME AND FOLLOW-UP

Follow-up at 3 months with the infectious diseases team showed that the patient had recovered well and had no residual symptoms. She had completed her course of antibiotics and anticoagulation, and there did not appear to be any lasting consequences.

DISCUSSION

From the perspective of a non-specialist clinician, the key question in Lemierre's syndrome is what processes are likely to result in rapid deterioration and hence require critical care and specialist team involvement. It is generally respiratory failure that prompts critical care involvement, and depending on the case series intensive therapy unit (ITU) admission rates can be as high as 60%–70%. Intubation is required in up to 37% of cases.^{9–10} There is an isolated report of an extremely severe case requiring extracorporeal membrane oxygenation.¹¹ Despite the dramatic pathophysiology, impairment of other organs (renal, cardiovascular, among others) tends to be transient, and cases requiring inotropic support and haemofiltration are accordingly rare.^{2–11}

It is generally accepted that the lungs are the most common site of septic metastasis¹⁰ with an incidence greater than 80% in some case series.² Lung involvement generally manifests early; it was present on the first day of septicaemia in some of Lemierre's 20 cases.¹ Respiratory symptoms have, on occasion, been cited as the presenting complaint for individuals subsequently diagnosed with Lemierre's syndrome.¹² Progression is often rapid with pleural effusion and empyema common even with early antibiotic therapy.² CT findings in the chest can be quite characteristic including lobar consolidation, pleural effusion and multiple peripheral pulmonary nodules. On occasion, there may also be evidence of cavitating abscess or empyema.^{2–12} The severity of respiratory consequences from Lemierre's syndrome is such that chest drain insertion and intubation may be required in order to combat worsening respiratory failure.¹³

Anticoagulation in Lemierre's syndrome is another key issue with no definitive answer due to the rarity of the disease and hence lack of large study populations and high-quality research. Bondy and Grant¹⁴ attempted to circumvent this shortcoming by consulting literature for similar conditions, namely pelvic septic thrombophlebitis and otogenic sigmoid sinus thrombophlebitis. Although they reached the conclusion that anticoagulation was appropriate in the acute setting and less so in the long term, their evidence base suffered similar flaws relying on slightly larger case studies and lacking randomised controlled trials or meta-analyses. Falagas *et al* conducted a systematic review of anticoagulation in septic deep vein thrombosis arising from pelvic veins, portal vein and IJV. They acknowledged similar issues relating to the lack of high-quality randomised controlled trials and concluded that failure of isolated antibiotic therapy or evidence of intracranial thrombosis should prompt anticoagulation.¹⁵ A recent Canadian case series in children aged 0–17 years described an individual who developed thrombotic complications secondary to non-compliance with anticoagulant therapy. Unfortunately, it neither specifies the complication nor the circumstances surrounding initial therapy and subsequent non-compliance.¹⁶

The exact mechanism by which septic embolisation occurs and the role of the IJV thrombus is not fully understood. It is believed that the clot acts as a reservoir for bacteria, protecting them from antibiotic therapy that is less able to penetrate the clot. Subsequent recanalisation of the IJV during the course of recovery is believed to permit increased penetration of antibiotics and hence increased therapeutic efficacy.¹⁷ This physiological theory has also been put forward for infective cavernous sinus thrombosis.¹⁸ This gives rise to two possibilities: breakdown of the clot could theoretically release septic emboli implying anticoagulation could worsen prognosis¹⁷ or alternatively earlier breakdown of the clot as a consequence of anticoagulation could permit better antibiotic penetration and faster resolution. There are case reports describing the use of mechanical thrombolysis in the treatment of Lemierre's syndrome and such treatment has not resulted in further septic emboli.¹⁹ Case reports in which anticoagulation therapy has been started following non-resolution with antibiotic therapy do demonstrate an improvement in patient condition following anticoagulant administration but it is impossible to determine whether this is solely due to the addition of an anticoagulant agent.¹⁷

Lemierre's original article cited multiple other primary infection sites leading to the septic emboli including the middle ear. In view of this, many recent articles have expanded their case definitions to include individuals with other ENT primary infections resulting in IJV thrombosis. Schubert *et al*²⁰ noted that while infections originating in the middle ear may spread to involve the intracranial vasculature, none of those originating in the oropharynx progressed past involving extracranial sites. There is, however, a case report of Lemierre's syndrome secondary to parapharyngeal abscess resulting in sigmoid sinus thrombosis. This occurred as a delayed presentation 6 weeks after discharge and was treated effectively with anticoagulation.²¹ Since patients have certainly been effectively treated without the use of anticoagulants at all, reserving their use for cases not resolving on appropriate antimicrobials seems a reasonable option. However, since the catastrophic possible consequence of Lemierre's

syndrome is intracranial thrombosis, and this has occurred several weeks after apparent successful treatment of the infective process, one could make an argument for the use of anticoagulation in all cases to mitigate this risk; careful balancing of the risks and benefits is essential.

Contributors TJS reviewed the patient's medical notes, conducted the literature review and wrote the manuscript. PJ reviewed the manuscript, provided editorial advice and assisted in placing the case in a critical care context.

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Learning points

- The diverse nature of presenting symptoms in Lemierre's syndrome means patients may present to multiple different specialties.
- Lemierre's syndrome is a multiorgan process with the potential for serious consequences.
- Early involvement of the critical care team allows the patient to be managed in an appropriately monitored and supported environment.
- Lemierre's syndrome should be considered in the differential for patients with upper respiratory symptoms who have significant clotting derangement or are disproportionately septic, especially if there are also symptoms in the neck.
- Anticoagulation in Lemierre's syndrome is a contentious issue and should be considered by specialist teams carefully on an individual basis.

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