Case Report

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Severe pneumonia and jaundice in a young man: an atypical presentation of an uncommon disease

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We present a patient with an atypical presentation of *Fusobacterium* infection, the genus responsible for Lemierre's syndrome. This syndrome, which often affects healthy, young people and can be fatal if not recognized and treated early, is defined as a history of recent oropharyngeal infection with clinical or radiological evidence of internal jugular vein thrombosis and isolation of anaerobic pathogens, mainly *Fusobacterium necrophorum*. The history, presentation, investigations and management of the patient are described and then contrasted with the existing literature surrounding Lemierre's syndrome, once termed the 'forgotten disease'.

Case report

A previously fit and well 26-year-old male presented to hospital with a 3-day history of severe sore throat, general malaise, non-bloody diarrhoea, vomiting, fever and headache. He had no significant past medical history, did not take any medications and had no known allergies. He was an electric engineer who worked with air conditioning units and was an occasional drinker, a non-smoker and lived with his fiancé, their two children and a dog. He had no history of foreign travel and no risk factors for blood-borne viruses.

On initial examination, the patient was clammy and febrile with jaundiced sclera. He had pharyngeal erythema and decreased air entry in the right lung base. Heart sounds were normal. He was tachycardic at 150 beats min⁻¹ but normotensive. He was tender in the right upper quadrant and right lower quadrant with a 3 finger breadth palpable smooth liver edge. Neurological examination was normal.

Initial blood tests revealed acute kidney injury with an estimated glomerular filtration rate of 32 ml min⁻¹, creatinine 207 µmol l⁻¹, urea 13.8 mmol l⁻¹ and bicarbonate of 19 mmol l⁻¹. Leukocytes were raised with a neutrophilia and C-reactive protein was 258 mg l⁻¹. Haemoglobin was 14.9 g dl⁻¹, platelets 79 × 10⁹ l⁻¹ and international normalized ratio 1.2. He had deranged liver function tests with a bilirubin level of 91 µmol l⁻¹, alanine aminotransferase 50 U l⁻¹, albumin 35 g l⁻¹ and alkaline phosphatase of 128 U l⁻¹. Glucose was normal and blood cultures were sent. A chest radiograph showed patchy linear opacities in the right lower zone. An electrocardiogram showed sinus tachycardia.

The initial diagnosis was community-acquired pneumonia. He was admitted under the medical team and treatment with intravenous fluids, co-amoxiclav and clarithromycin was initiated.

The following day, the patient continued to be pyrexial, his oxygen requirements increased and he was referred to the Infectious Diseases team. On review, he had a PaO₂ of 10.14 kPa on 35 % FiO₂ with normal PCO₂ and pH, indicating type 1 respiratory failure with a wide arterial–alveolar gradient. Temperature was 40 °C and he remained tachycardic at 140 beats min⁻¹. He was noted to have pain in the right side of the neck with ipsilateral swelling on examination. *Legionella* and pneumococcal urinary antigen were negative. Renal function was improving but leukocytes and C-reactive protein remained raised. It was felt that the patient was septic with multi-organ involvement, and a diagnosis of Lemierre's syndrome was considered. Co-amoxiclav was changed to tazocin (tazobactam and piperacillin) intravenously, and prophylactic enoxaparin was commenced. Clarithromycin was continued. An arterial line was inserted and PaO₂ was 19.6 kPa on 60 % FiO₂, indicating a further widening of the arterial–alveolar gradient. The patient was counselled for blood-borne virus screen including HIV. He was moved to a high dependency unit, and although imaging investigations for endovascular thrombosis and liver/pulmonary abscesses were entertained, he was considered too unstable to move to the radiology department.

On day 3 of admission, a repeat chest radiograph showed that consolidation now involved the right mid and lower zone. Inflammatory markers, leukocytes and renal function were improving but O₂ requirements remained high. The patient had a high bilirubin, low platelets and a drop in haemoglobin to 11.2 g dl⁻¹. Blood film showed thrombocytopenia with large platelets and reactive neutrophil leucocytosis, but no polychromasia, spherocytes or fragmentation.

Oxygen requirements stabilized over the following 3 days. On day 4, a Gram-negative rod was seen in the anaerobic blood culture and metronidazole was added to the antibiotic regimen. Cultures grew two anaerobic colonies of differing morphology so further purity plates were

Abbreviation: IJV, internal jugular vein.

prepared. A repeat chest radiograph and subsequent thoracic ultrasound showed a small right-sided pleural effusion. Atypical pneumonia serology and HIV test were negative. A transthoracic echo was performed due to a new systolic murmur but was normal.

One week into admission, the Gram-negative rod was identified on both purity plates as *Fusobacterium nucleatum* via Rapid ID 32 A testing (bioMérieux). This was confirmed with a certainty of 91.7% via the API Web (bioMérieux) program and T value of 0.97 with no other alternative identification suggested. Molecular 16S rRNA gene sequencing was not performed. The isolate was confirmed as sensitive to penicillin with an Etest MIC of $<0.02 \text{ mg l}^{-1}$ ($<0.25 \text{ mg l}^{-1}$ classed as sensitive and $>0.5 \text{ mg l}^{-1}$ as resistant according to the European Committee on Antimicrobial Susceptibility Testing, 'EUCAST'). No other resistance profiling was performed as: ampicillin, amoxicillin and piperacillin sensitivity was inferred from the penicillin Etest result, which indicated a non- β -lactamase producer (EUCAST, 2011); metronidazole resistance is rare; and clarithromycin has no activity against *Fusobacterium* species. He was switched to benzylpenicillin (raised liver enzymes were suggestive of a drug reaction to piperacillin/tazobactam) and he was continued on metronidazole (see Table 1). An ultrasound scan of the neck veins showed no internal jugular vein (IJV) thrombosis. Urine and stool culture and microscopy were unremarkable. A throat swab was requested but not processed. CT thorax showed bilateral pleural effusions and consolidation but no evidence of septic emboli. The patient continued to improve and was discharged home 11 days after admission on oral co-amoxiclav having had 10 days of intravenous therapy. He was seen 2 weeks later in the outpatients' department, with complete clinical and radiological improvement.

Discussion

André Lemierre first described a series of 'postanginal septicaemia' cases in the *Lancet* in the 1930s (Lemierre, 1936). Prior to widespread antibiotic availability and usage, the mortality rate in his series was high with 18 out of 20 patients dying. Lemierre's syndrome – also known as 'necrobacillosis' or 'anaerobic tonsillitis' – comprises

history of recent oropharyngeal infection with clinical or radiological evidence of IJV thrombosis and isolation of anaerobic pathogens, mainly *Fusobacterium necrophorum*.

Microbiologically, Lemierre's syndrome is caused by anaerobic mouth commensals which spread from the oropharynx, sinuses or ear canal into local tissues, the IJV and then seed to disseminate to other organs. It is, therefore, essential when considering the diagnosis to examine ear, nose, throat and dentition with care. A recent systematic review found that *F. necrophorum* accounts for 57% of cases, *Fusobacterium* spp. 30%, *F. nucleatum* – also associated with acute ulcerative gingivitis – 3%, with anaerobic streptococci and other Gram-negative anaerobes comprising the remainder (Karkos *et al.*, 2009). These Gram-negative spindle-shaped bacteria have potent virulence factors leading to gross inflammation, neutrophil activation and promotion of thrombus formation associated with raised levels of antiphospholipid antibody and factor VIII (Han *et al.*, 2003; Goldenberg *et al.*, 2005).

With the rise in use of penicillin, the frequency of the syndrome declined over the following years until it came to be termed the 'forgotten disease' (Weesner & Cisek, 1993). However, the past decade has shown an increase in the incidence of the disease, especially amongst the paediatric population (Goldenberg *et al.*, 2005). This is thought to be due to increased prescription of macrolides for acute pharyngitis (Ramirez *et al.*, 2003). Indeed, some series have shown rates of endemic pharyngitis caused by *F. necrophorum* to be similar to that caused by group A β -haemolytic streptococci with authors urging avoidance of macrolides – which have little activity against *Fusobacterium* species – in any antibiotic treatment of non-streptococcal pharyngitis (Centor, 2009). Another explanation for the increased incidence may also be due to advances and improvements in anaerobic cultures.

The disease mainly affects young, healthy adults, beginning with a sore throat. It can then progress to the syndrome described above with a prominent sign being neck pain, often unilateral. If not recognized and treated promptly and appropriately, suppurative thrombophlebitis and disseminated infection may develop with complications such as lung failure (septic emboli, pneumonia, acute

Table 1. Patient's inflammatory markers, liver function test, leukocyte count and antibiotic regimen during admission

Day of admission	$10^{-9} \times$ Leukocytes (l^{-1})	$10^{-9} \times$ Neutrophils (l^{-1})	Bilirubin ($\mu\text{mol l}^{-1}$)	Alanine aminotransferase (U l^{-1})	Alkaline phosphatase (U l^{-1})	C-reactive protein (mg l^{-1})	Antibiotics used
1	15.3	13.6	91	50	128	258.4	Co-amoxiclav/clarithromycin
2	14.9	12.0	82	36	79	233.2	Tazocin/clarithromycin
4	12.2	9.6	49	21	76	128.3	Tazocin/clarithromycin/ metronidazole
7	12.0	9.0	14	169	176	43.9	Benzylpenicillin/metronidazole
11	10.1	7.5	13	107	150	7.1	Co-amoxiclav

respiratory distress syndrome), renal failure, haematological failure (microangiopathic consumption coagulopathy, thrombocytopenia), abscesses (brain, subdural, epidural) and cavernous sinus thromboses, which cause significant morbidity and mortality. Rarer complications in the literature include endocarditis (Vedire *et al.*, 2007), pyomyositis (Crum-Cianflone & Mayer, 2008) and noma (Falkler *et al.*, 1999).

Culturing pharyngeal swabs and blood is clearly an important element in diagnosing infection with *Fusobacterium* but also of importance is imaging for potential thromboses. With regard to IJV thrombosis, this can be undertaken by ultrasound scan but, in the stable patient, CT with contrast would be the optimum investigation to identify such thrombi. It may be argued that it would have been beneficial for our patient to have had inclusion of his neck in his initial CT thorax to look for IJV thrombosis.

There have been no randomized controlled trials into effective management of Lemierre's syndrome but a prolonged course of – initially intravenous – antibiotics and surgical intervention (for removal of propagating clots or debridement of pulmonary cavities and empyema) is advised (Alifano *et al.*, 2000). Penicillins can be used in the treatment of Lemierre's syndrome but, due to concern regarding treatment failures in Lemierre's syndrome caused by β -lactamase-producing *F. necrophorum* and *F. nucleatum*, antibiotics such as co-amoxiclav, tazocin, metronidazole and clindamycin are recommended (Appelbaum *et al.*, 1990; Brook, 1993). In our patient, tazocin was used for a few clinical reasons: the diagnosis of Lemierre syndrome had been questioned, which can often be polymicrobial, and the possibility that the presentation was still down to either severe community-acquired pneumonia or Gram-negative sepsis. With regard to anticoagulation, there is still debate surrounding its role in these cases given the lack of trial data in this area (Bondy & Grant, 2008). Within other specialties, septic emboli are treated with anticoagulation but no controlled studies have been conducted in Lemierre's syndrome patients with IJV thrombosis. However, descriptive studies have revealed that a high proportion of patients with Lemierre's syndrome are initiated on anticoagulation for 3–6 months – up to 89% in paediatric cases (Goldenberg *et al.*, 2005; Alvarez & Schreiber, 1995). Given the lack of trial data, the decision to initiate anticoagulation will likely be made on the basis of expert opinion and experience, and should take into consideration the benefits and drawbacks to the individual case concerned (Hoffman *et al.*, 2010).

Our patient fulfilled the diagnostic criteria with recent oropharyngeal infection, clinical suspicion of IJV thrombosis on initial review and subsequent microbiologically confirmed *F. nucleatum* culture. However, there are a number of features in our patient's presentation that are atypical. He was frankly jaundiced with pneumonia on admission. It is known that up to a third of patients with Lemierre's syndrome will have deranged liver function tests

including hyperbilirubinaemia but frank jaundice is uncommon (Chirinos *et al.*, 2002). The patient was clearly septic with a right basal pneumonia and type 1 respiratory failure. Despite having right-sided neck pain and swelling suggestive of IJV thrombosis, he had no evidence of suppurative thrombophlebitis or septic thromboemboli on ultrasound scan of the neck or CT thorax. It may be postulated that this was due to early presentation of the patient, early initiation of appropriate intravenous antibiotics, and – possibly, although the issue remains contentious – early use of subcutaneous low-molecular-mass heparin. Another unusual feature was the organism isolated: *F. nucleatum*. This is an uncommon cause of Lemierre's syndrome (approx. 3%), the virulence and progression of which is likely to be similar to that of *F. necrophorum* although there is little evidence available to confirm this. Our case highlights the importance of both appropriate and prolonged anaerobic culture to identify the organism responsible and, additionally, timely and suitable antibiotic prescription when Lemierre's syndrome is suspected. In our patient, the diagnosis was considered and treated when he fulfilled two of three of the diagnostic criteria (recent history of oropharyngeal infection and clinical evidence of IJV thrombosis) and organism identification was only achieved 1 week after blood cultures were sent. Moreover, once the diagnosis has been made it may be essential to involve multiple appropriate specialties in order to manage potential complications. These may include microbiologists; infectious diseases physicians; intensivists; radiologists; and ear, nose and throat or vascular surgeons (for abscess drainage and thrombus intervention if required).

It is likely that, in this antibiotic era, the classical presentation and signs of Lemierre's syndrome may not be present. Our patient's presentation and development are supported by a review by Chirinos *et al.* (2002), which indicated that the more common presentation of *Fusobacterium* sepsis is with pharyngitis, a tender or swollen neck and noncavitating pulmonary infiltrates. Indeed, the complication rates from this disease have fallen, as have the mortality rates, which were over 90% in the pre-antibiotic era but are approximately 5% in the present day (Chirinos *et al.*, 2002; Koay *et al.*, 1995).

Summary

It is essential that clinicians consider the diagnosis of Lemierre's syndrome early in septic patients with pharyngitis and neck pain, especially in situations where antibiotics that have no activity against fusobacteria – such as macrolides – have been used previously without effect. However, it must be remembered that the classical features of Lemierre's syndrome are not as common in modern day medicine: our patient presented with severe pneumonia and jaundice. Once suspected, appropriate extended cultures must be taken, antibiotics initiated promptly and the patient managed in an appropriate care setting with multi-specialty

involvement. Lemierre's syndrome has not been forgotten but it may present atypically.

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