



Case Report

SEPTIC THROMBOPHLEBITIS OF INTERNAL JUGULAR VEIN AND PULMONARY EMBOLISM: LEMIERRE'S SYNDROME, A FORGOTTEN BUT PRESENT LIFE-THREATENING COMPLICATION OF ACUTE PHARYNGO-TONSILLITIS

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ABSTRACT

Lemierre's Syndrome is characterized by clinical or radiological evidence of suppurative thrombophlebitis of the internal jugular vein with a history of recent oropharyngeal infection and can be complicated by septic systemic embolism. The disease is usually caused by Gram-negative anaerobic organisms, mainly *Fusobacterium necrophorum*. Once called the forgotten disease in the pre antibiotics era, it may not be that uncommon after all. We report a case of Lemierre's Syndrome in a 14-year-old patient, with a blank medical history, with an oropharyngeal infection and onset of neck and thoracic pain. Computed tomography of the neck and thorax showed a thrombophlebitis of the internal jugular vein and septic emboli in the lungs. *F. necrophorum* was isolated from blood cultures. The isolated *F. necrophorum* showed susceptibility to metronidazole, clindamycin and betalactam/ beta-lactamase inhibitor combinations with no signs of resistance or reduced sensitivity, so prolonged multidrug therapy was considered the mainstay of treatment. Anticoagulation is believed to play a favourable role in the recovery of the disease because of the potential for faster resolution of thrombophlebitis, but the use of anticoagulation is still heavily debated due to conflicting results in literature. Lemierre's Syndrome is an unfamiliar syndrome, once considered rare, with an increasing number of reported cases recently. It is due to septic complications of oropharyngeal infections, which lead to thrombophlebitis of the internal jugular vein with potentially fatal complications occurring primarily in young, otherwise healthy individuals, which requires a prompt diagnosis and treatment. In this case report, we present a case of Lemierre's Syndrome in a 14-year-old

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patient treated with long-term antibiotic and anticoagulant therapy, considering the young age and the extent of the septic emboli to lungs, with complete resolution of the disease at the end of the treatment.

KEYWORDS: *Lemierre's Syndrome, thrombophlebitis, internal jugular vein, septic emboli, case report*

INTRODUCTION

In 1936 André-Alfred Lemierre reported on a series of 20 cases of postpharyngitis sepsis, of whom only 2 survived. The syndrome, diagnosed by a combination of clinical signs, positive blood cultures and radiological findings, classically comprises pharyngeal infection, internal jugular vein septic thrombosis, producing disseminated emboli to the periphery (often septic pulmonary emboli) and the presence of the anaerobic bacterium *Fusobacterium necrophorum* in blood culture (1, 2). This condition was eventually named after Lemierre's syndrome.

Lemierre's Syndrome usually begins as a local oropharyngeal infection and presents with fever, cough, sore throat and neck swelling. Later during the course, after the throat had settled, infection spreads via blood stream to other organs (the venous thrombosis is likely the result of endothelial dysfunction caused by inflammatory factors from the local infection) and led to overwhelming systemic infection (3). Lemierre recognized the importance of the progression from thrombophlebitis of the tonsillar veins to internal jugular vein thrombophlebitis with subsequent septicemia due to the release of small pieces of infected thrombus (4). This spread of septic emboli may produce lung lesions (lungs are affected in up to 85% of cases) that commonly appear as necrotic cavitory lesions but can also present as infiltrates, pleural effusions, empyema, lung abscesses, and necrotizing mediastinitis and patients can develop acute respiratory distress syndrome that requires mechanical ventilation (5, 6). Less commonly the hematogenous spread may involve joints, liver, spleen, kidneys and muscles (7).

Several authors highlighted that septic thrombophlebitis was also a feature of *F. necrophorum* infection in other sites, such as otogenic infection, having a higher incidence of intracranial complications, iliac vein thrombophlebitis associated with post-prostatectomy infection, portal vein thrombophlebitis associated with infection secondary to rectal carcinoma, and mesenteric thrombophlebitis after an appendectomy. Stimulating clot formation and multiplying in the clot with subsequent embolic spread is clearly a fundamental feature of the pathogenesis of *F. necrophorum* infection (8,9).

Although uncommon, clinicians need to be aware of this condition because patients with Lemierre's Syndrome require prompt and appropriate therapy.

CASE REPORT

We describe the case of a fourteen-year-old female patient who accessed the ER because of sore throat, fever and chest pain. Her clinical history was silent. She has presented a sore throat for four days and a fever for three days with peaks up to 40°C. She was therefore taken to her general medicine practitioner, who prescribed her an oral antibiotic with clarithromycin for pultaceous tonsillitis. After one day without improvement, her doctor advised her to switch to a therapy with amoxicillin-clavulanate, with an improvement in her symptoms. The same night, however, she woke up with chest pain localized on the right shoulder and in the scapular region bilaterally, which worsened with deep inspiration and was only mildly responsive to ibuprofen. For this reason, she accessed an ER in a peripheral hospital, where a nasal-pharyngeal swab for Sars-cov-2 (negative) and blood samples (mild increase in inflammation markers, CRP 69 mg/L, WBC 13.360/mmc) were performed. ECG and chest X-Ray were unremarkable.

At the ENT evaluation, hypertrophy and medialization of the left tonsil with a laterocervical lymphadenopathy was diagnosed. The patient was therefore admitted in the Paediatric ward to start endovenous administration of amoxicillin-clavulanate, which the next day was changed to ceftriaxone. A bedside ultrasound showed multiple reactive lymphnodes in



Fig. 1. Neck ultrasound showed venous blockage in the internal jugular vein by a thrombus (circle).

the left laterocervical region and the nasal-pharyngeal swab culture revealed no pathological microorganism growth. The day after a new US was then performed, which confirmed the presence of left lymphadenopathy but also showed a poorly compressible left internal jugular vein, suggesting a jugular vein thrombosis (Fig. 1).

In light of all these findings a diagnosis of Lemierre's Syndrome was suggested, which was confirmed by an urgent neck CT scan which showed thrombophlebitis of the left internal jugular vein, multiple ovalar lymphnodes in the left laterocervical region, at the mandibular angle and in the sovraclavear compartment bilaterally (Fig. 2). Lung CT scan was also performed and showed bilateral cavitated pulmonary nodules, as result of metastatic septic emboli (Fig. 3).

The patient was therefore transferred the University Hospital of Verona and admitted in the Paediatric ward under the ENT team care. She was administered an anticoagulant therapy with Enoxaparin at the therapeutic range of 5000UI. The antibiotic therapy was set with ceftriaxone 2g/die and clindamycin 600g/die, substituted the next day according to the infective disease consult with metronidazole 500 mg x3/die. After ten days of antibiotic and anticoagulant therapy, symptoms and inflammation markers were back to normal. The neck US showed patency of the left internal jugular vein.

The patient was discharged with a prescription of Enoxaparin for three months and oral amoxicillin-clavulanate 1g x 3/die for a month, until the follow-up CT scan programmed after one month. This confirmed patency of the vein and showed that the pulmonary nodules were diminishing in number and size (Fig. 4). The patient's conditions were evaluated every month for 6 months both clinically and with blood tests. A tonsillectomy was also scheduled in order to prevent the recurrence of the condition.

DISCUSSION

Lemierre's Syndrome is an uncommon disease of the postantibiotic era but can carry dangerous potential sequelae with a high mortality rate. In the past the syndrome was common, but with the widespread use of antibiotics for upper respiratory tract infection in the 1940s, the incidence of the syndrome dropped, and it eventually became known as the "forgotten disease" (10). Since the 1990s, however, there has been a marked resurgence of Lemierre's syndrome, and it is unclear if this rising trend in cases is due to advancement in diagnostic techniques, restriction in antibiotic use for sore throat, decreased number of tonsillectomies or increased antibiotic resistance to organisms. It is usually seen among young adults, with the highest incidence between 15-25 years of age, and according to a Danish study made by analysing all the cases from 1998 to 2001, the annual incidence among individuals aged 14 to 24 was 14.4 cases per million people while the incidence in the whole population was 3.6 cases per million people (11).

Little is known regarding the reason for this age distribution with possible reasons linked to anatomy, hormonal changes, social behavior (human to human oral contact), co-infections and the presence of tonsils (reaching their largest size in puberty) (12). Lemierre's Syndrome refers to septic

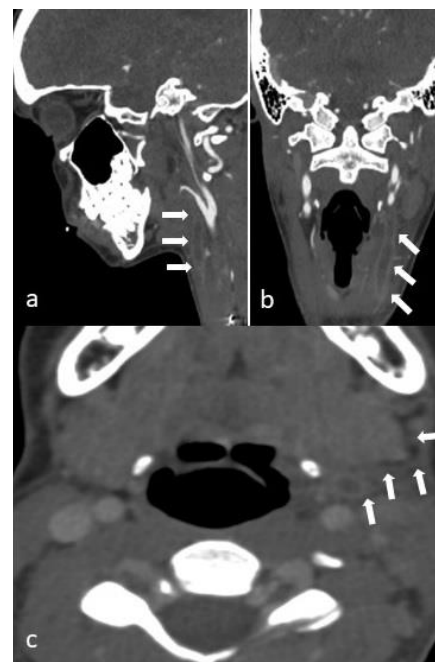


Fig. 2. Contrast-enhanced CT of the neck region with axial, coronal and sagittal reconstruction showing a hypoechoic thrombus in the middle and distal tract.

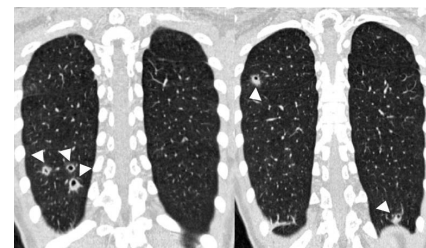


Fig. 3. Chest computed tomography (CT) with coronal reconstruction (A and B) demonstrating multiple bilateral pulmonary nodules, most of which were cavitated and associated with areas of consolidation (arrows).

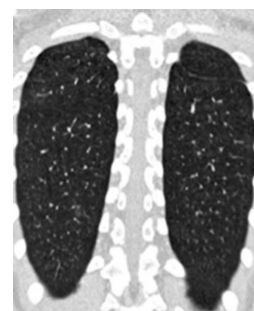


Fig. 4. After 4 weeks of treatment, repetition of chest CT scan showed resolution of pulmonary localisations.

thrombophlebitis of the internal jugular vein (IJV) and despite its nonnegligible annual incidence of $> 1/100000$, often goes undiagnosed due to its non-specific symptoms (13). The syndrome typically begins with an oropharyngeal infection, usually in association with tonsil or peritonsillar involvement. Other antecedent conditions include oral cavity or dental infections, mastoiditis, otitis or infectious mononucleosis (14). Lemierre's Syndrome is caused by bacteria that invade the pharyngeal mucosa and lateral pharyngeal space, inflammation within the wall of the vein and infected thrombus within the lumen resulting in subsequent internal jugular vein septic thrombophlebitis and metastatic infections, due to disseminated emboli to the periphery (often septic pulmonary emboli) (15,16).

The most commonly associated organism, *F. necrophorum*, is a gram-negative, anaerobic bacterium that is part of the normal flora of the oropharynx, but the recent development of various antibiotics and advancements in medical care have led to diversified and antibiotic-resistant strains, therefore multiple other bacteria have been implicated in Lemierre's Syndrome, such as *Streptococcal species*, *Eikenella corrodens*, and *Staphylococcus aureus* (17).

A multidisciplinary approach is necessary to treat patients with Lemierre's Syndrome. Collaboration with infectious disease experts, radiologists and otolaryngologists is essential to reach a prompt diagnosis and achieve a good therapeutic outcome, in order to prevent its devastating effects (18).

Antibiotic therapy is the mainstay of treatment. *F. necrophorum* shows *in vitro* susceptibility to metronidazole, clindamycin, beta-lactam and carbapenems. Any antimicrobial regimen should include a b-lactamase inhibitor, because b-lactamase-producing strains of *F. necrophorum* have been reported and co-infecting pathogens might also produce b-lactamases (19). One review showed that metronidazole was the most commonly prescribed antibiotic; it shows excellent penetration into most tissues and can be administered orally without compromising bioavailability.

In vitro data have shown that metronidazole or carbapenem shows greater bactericidal activity against *F. necrophorum* than clindamycin (20). *F. necrophorum* is intrinsically resistant to macrolides, fluoroquinolones, tetracyclines, and aminoglycosides (22,21). A review of 100 *F. necrophorum* isolates from 1990 to 2000 revealed that all strains were susceptible to metronidazole, clindamycin, imipenem, amoxicillin-clavulanate, and cefoxitin and 15% of strains were resistant to erythromycin. The level of 15% resistance to erythromycin may be important as this drug or its newer derivatives are regularly prescribed by primary care physicians for the treatment of upper respiratory tract infections (20-22). Antimicrobial therapy should be prescribed for 3-6 weeks. Once the infection is controlled, therapy can be completed orally.

Despite providing appropriate antimicrobial treatment, the observed clinical response might be slow. One explanation for the slow response is that Lemierre's Syndrome is an endovascular infection and that antibiotics have difficulty in penetrating the fibrin clot (23, 24). Theoretically, a septic thrombus sequesters bacteria and creates a barrier to antibiotic penetration. When the thrombus is dissolved by anticoagulants, the bacteria are exposed to a higher concentration of antibiotics, increasing accessibility (20, 23, 24).

On the other hand, the role of anticoagulation in the treatment of Lemierre's Syndrome is more uncertain and it is not clear its effect on the recanalization of the vessels. Due to a lack of high-level evidence there is no current consensus

(25). Some physicians believe that it is possible to achieve the dissolution of the thrombus simply by using antibiotics, since it originated from an infection. Other physicians instead confirm that anticoagulation plays a favourable role in the recovery of the disease because of the potential faster resolution of thrombophlebitis and the prevention from other complications, such as cavernous sinus thrombosis or pulmonary embolism (13). Theoretically speaking, behind these two opposite ideas, there is the thought that, given that the thrombus sequesters bacteria, with anticoagulants there is the risk of increasing the bacteraemia and of causing more septic emboli, but on the other hand it is also possible to increase the effect of the antibiotics (13).

Many studies or reviews indicate a favourable outcome both with and without anticoagulation. Despite this, there is an increase in use of anticoagulant in treatment of Lemierre's Syndrome over the last few years. In older reviews 21-23% of patients were given anticoagulants (26, 27) in contrast to the reviewed population of Johannesen et al. and Rebelo et al. (64% and 100% resp.) (26, 28).

A recent meta-analysis examined 394 patients treated for Lemierre's Syndrome between 1980 and 2017 but failed to find a statistically significant improvement in vessel recanalization and mortality using anticoagulants (25). Many recent cases, especially considering the pediatric population, reported the use of some form of anticoagulants which seemed to have reduced or slowed the progression of thrombosis (29). The use of anticoagulants is still questionable and randomized

clinical trials should be set in order to identify the optimal anticoagulant therapy.

Even the duration of the anticoagulation is debated, but it is probable that it is indicated for at least six weeks due to the concomitant embolic disease (30, 31). For example, Goldenberg et al have analyzed the outcome of 8 patients treated with anticoagulants for a median duration of 3 months (range: 7 weeks-1 year) noticing the complete recovery from the disease and no recurrent thromboembolism or anticoagulant-associated major hemorrhage after one year of follow up (32).

Therefore, the treatment should be tailored for every patient considering his clinical status, the kind of disease complications and the improvement obtained from the therapy. This is why an adequate follow up should be set, providing US of the neck or CT scans to monitor the recanalization of the internal jugular vein and regular blood tests to analyze the inflammatory markers. In the literature there is no consensus on how long the follow up should be and on how often the clinical evaluations should be organized. However, it seems common to repeat the imaging after one or two months and to monitor the patients for no more than six months or one year.

Finally, surgical treatment of the thrombosis is very seldomly indicated and the internal jugular ligation or excision is rarely performed. The main function of surgery is to drain the cervical abscess, commonly in the peritonsillar and lateral pharyngeal region, and to treat possible complications such as lung empyema or septic joints (29).

CONCLUSIONS

Lemierre's Syndrome is now a rare entity which can be fatal. It is a bacterial condition, mostly caused by *Fusobacterium necrophorum*, with systemic complications which can be fatal, and it should be suspected in young people with persistent fever and neck pain and/or distal metastatic septic lesions. Contrast-enhanced computed tomography of the neck is the best diagnostic method as it detects vascular thrombosis of the internal jugular vein and other complications such as pulmonary emboli. A multidisciplinary approach is necessary to treat patients with Lemierre's Syndrome. Collaboration with infectious disease experts, radiologists and otolaryngologists is essential to reach a prompt diagnosis and achieve a good therapeutic outcome, in order to prevent its serious long-term complications, including neurologic deficits and debilitating conditions potentially requiring long and resource-intensive additional care.

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