

LEMIERRE'S SYNDROME: CASE REPORT OF 'THE FORGOTTEN DISEASE' IN CURRENT COVID-19 PANDEMIC

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Abstract

Lemierre's syndrome refers to infectious thrombophlebitis of the internal jugular vein developed as complication of an oropharyngeal infection. It is a rare syndrome, affecting otherwise healthy young adults, which may lead to sepsis complicated by septic embolization. Although there is a characteristic clinical picture, many modern physicians are unaware of this syndrome, leading it to be termed 'the forgotten disease'. The authors report a case of late diagnosis due to initial suspicion of COVID-19 and highlight the pitfalls on its diagnosis.

INTRODUCTION

Lemierre's syndrome (LS) refers to infectious thrombophlebitis of the internal jugular vein (IJV) developed as complication of an oropharyngeal infection. It is a serious condition which may lead to severe sepsis complicated by septic embolization. Lungs are the most common site of septic embolization, most cases presenting with pneumonia or pleural empyema.¹⁻⁷ LS was named after the French bacteriologist, André Lemierre, who in 1936 first reported 20 cases of this syndrome.² It is most frequently caused by the anaerobic gram-negative bacterium, *Fusobacterium necrophorum*, which is part of the normal oral flora and has been shown to aggregate human platelets. Other bacteria have been identified, but these are atypical.^{1,3} While common in the pre-antibiotic era, LS is now rare, with an incidence of 1-4 cases per million.^{1,4} LS affects more com-

monly otherwise healthy young men, with a 2:1 male-to-female ratio.^{1,4,5} Although the clinical picture is characteristic, many clinicians are currently unaware of LS, leading it to be termed 'the forgotten disease'.^{4,8} Initial signs and symptoms include odynophagia, fever and easy fatigue which may simulate novel coronavirus SARS-CoV-2 disease (COVID-19). Treatment with broad spectrum intravenous antibiotics should be started promptly.⁵⁻⁸ In the presence of an abscess, surgical drainage should be considered. In cases of persistent sepsis or repeated septic embolization, surgical ligation or excision of the IJV should be considered.^{4,8} Currently, the most controversial role in LS management is anticoagulation due to the lack of controlled studies.³⁻⁶ Prognosis has much improved in comparison to pre-antibiotic era (90% mortality rate), with case series reporting mortality rates ranging from 0-18%.^{1,4} According to our search in Medline, since 2004, there are only six cases of LS

reported in Portugal.^{1,7-11}

CASE REPORT

In April 2020 a 37-year-old woman presented to our hospital with left-sided neck pain, odynophagia and fever. Diagnosis of exudative tonsillitis was made and she was discharged with oral clarithromycin (250 mg b.i.d.). COVID-19 nasopharyngeal swab test was negative. One week later, due to persistent fever, dyspnea, thoracalgia and easy fatigue, she returned. Blood samples showed increased white-cell-count (17.150/ μ L), thrombocytopenia (76000/ μ L) and increased C-Reactive-Protein (378 mg/L). On chest computed tomography (CT), diffuse areas of pulmonary opacities were considered

pulmonary manifestations of COVID-19 (Figure 1). Azithromycin and hydroxychloroquine were started, as advocated in the beginning of the pandemic. On the 4th day of hospitalization considering 3 negative COVID-19 tests, hydroxychloroquine was abandoned. Due to aggravating pneumonia and pleural effusion (Figure 2), antibiotherapy was changed to doxycycline plus ceftazidime and a thoracocentesis was performed. On the 7th day, due to persistent cervical pain and tumefaction, contrast-enhanced cervical CT was ordered showing peritonsillar thickening, emphysema and thrombosis of the left IJV (Figure 3). Diagnosis of LS was made and antibiotherapy was changed to Piperacillin-Tazobactam (4500 mg t.i.d.) for anaerobic coverage. Anticoagulation was started with Enoxaparin (60 mg b.i.d.). Blood cultures, pleural cultures, Coxiella Brunetti sero-

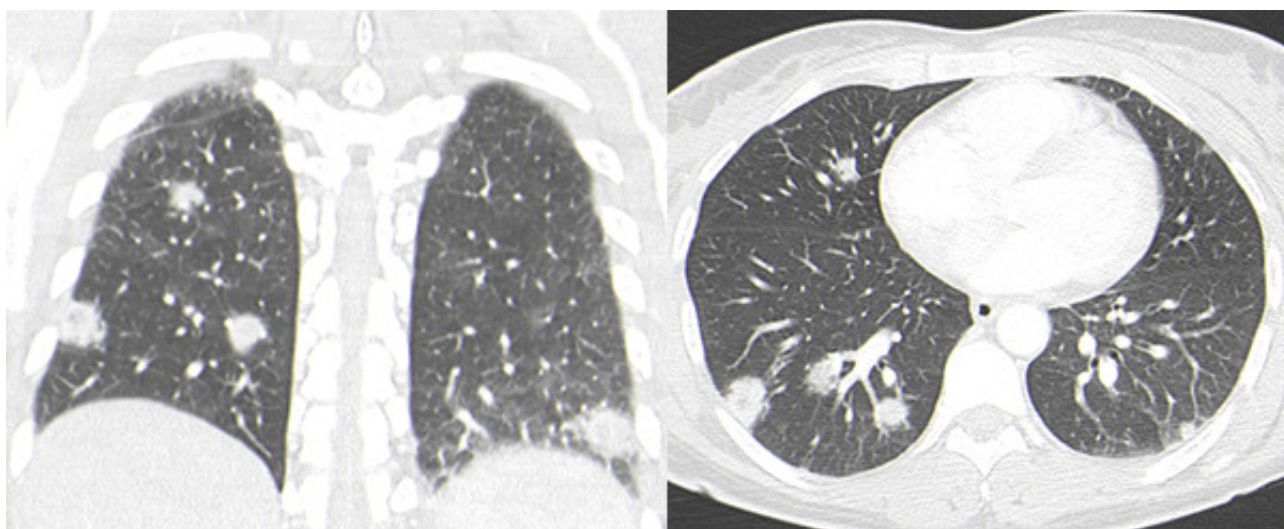


Figure 1 Diffuse areas of pulmonary opacities: coronal and axial views of chest computed tomography on admission.

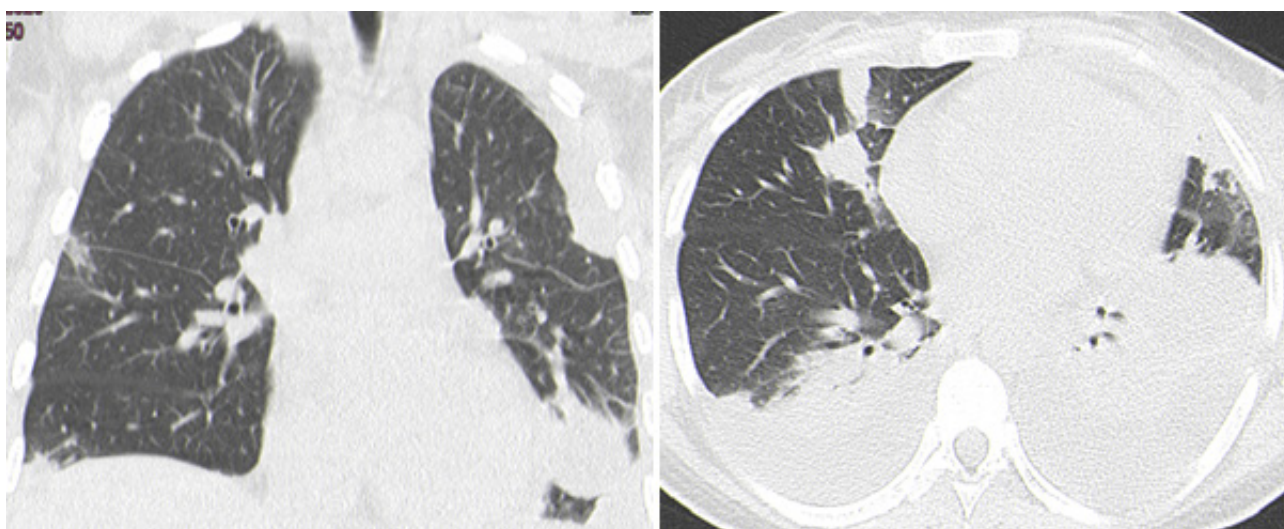
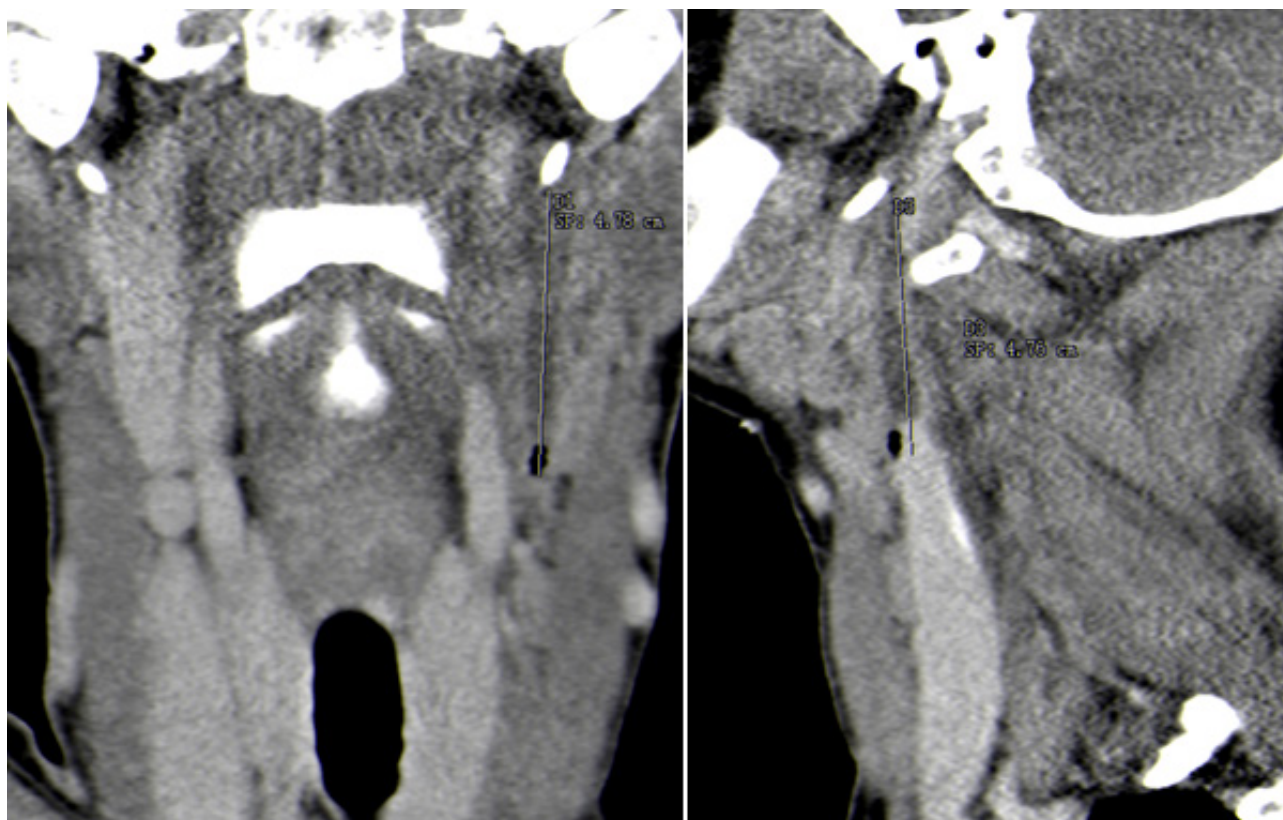


Figure 2 Aggravating pneumonia and bilateral pleural effusion: coronal and axial views of chest computed tomography on the 4th day of hospitalization.


Figure 3

Septic thrombophlebitis of the left internal jugular vein: coronal (4.78 cm) and sagittal (4.76 cm) views of contrast-enhanced cervical computed tomography.

logic test, Legionella and Pneumococcus antigens tests were negative. In the following 2 weeks, inflammatory markers declined to normal and a reduction in pulmonary opacities was observed. The last 3 weeks of antibiotherapy were completed under ambulatory hospitalization (total of 5 weeks). Screening for thrombophilia was negative. Anticoagulation was maintained with Rivaroxaban (20 mg q.d.) completing 4 months in total, but occlusion of the IJV persisted. To date, 1 year after discharge, the patient remains asymptomatic, with no recurring symptoms.

DISCUSSION

Diagnosis of LS is based on three criteria: oropharyngeal infection, IJV thrombophlebitis and septic embolization. The authors report a classic presentation preceded by tonsillitis: sore throat (reported in 82.5% cases), fever (82.5-100%), left tenderness/swelling at the mandibular angle, the 'cervical cord sign', suggestive of IJV thrombosis (25-45%), dyspnea and pleuritic thoracalgia.^{4,8} On chest CT, areas of diffuse pulmonary opacities without ground-glass appearance were consistent with septic pulmonary embolization and not COVID-19.¹²

Although clinical picture was typical, due to the low incidence and unawareness for LS in the current post-antibiotic

era, similar to most cases reported in the literature, diagnosis was late: 'the forgotten disease'.⁴⁻⁸ Furthermore, this case occurred during the first spike of COVID-19 pandemic, in one of the most affected regions in Portugal (Tâmega e Sousa). The use of personal protective equipment probably hindered thorough physical examination and only on the 7th day of hospitalization, as the patient condition continued to deteriorate, was the 'cervical cord sign' detected.

Although there was no confirmation, both thrombocytopenia and negative cultures support *Fusobacterium necrophorum* as the etiological agent. Its platelet aggregation activity and difficult culturing, typical of anaerobes, explain the forementioned results.^{4,5,8} In addition to this, only when antibiotherapy was scaled to Piperacillin-Tazobactam was clinical improvement noted. Indeed, *Fusobacterium necrophorum* is intrinsically resistant to macrolides, fluoroquinolones and tetracyclines and β -lactamase-producing strains have been reported.^{5,6} In our case, antibiotherapy was kept for a total of 5 weeks, which goes in line with the recommended 3-6 weeks to achieve appropriate penetration into fibrin clots.⁵

The role of anticoagulation as an adjuvant to antibiotherapy remains controversial. A recent meta-analysis did not demonstrate a statistically significant effect on mortality for patients treated with anticoagulation versus patients not an-

ticoagulated.³ However, due to the lack of controlled studies, anticoagulation is still recommended in cases of thrombus extension to the cavernous sinus, coexisting thrombophilia, failure to improve in the first 72 hours and large/bilateral clots.^{4,6,10} Our patient fulfilled the last two indications. After 4 months of anticoagulation, vessel recanalization was not observed, but this also goes in line with the findings by Gore.³

Surgical management in LS is rarely indicated. Persistent sepsis or repeated septic embolization are the main indications for ligation/resection of the IJV.^{4,8,10} In our case, since there was significant improvement following antibiotic and anticoagulation therapy, surgical treatment was not required.

Besides pulmonary complications, other complications include septic arthritis, osteomyelitis, meningitis, endocarditis and pericarditis.^{4,5,8} In our case, none occurred.

In conclusion, in an otherwise healthy patient with former oropharyngeal infection presenting with pneumonia, LS should be suspected. Prompt broad spectrum antibiotic treatment with anaerobic coverage should be started. In the event of persistent sepsis or large thrombosis, anticoagulation as an adjuvant to antibiotherapy may be considered.

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