

**Lemierre's Syndrome: an atypical co-infection by *Staphylococcus aureus*
and *Mycobacterium tuberculosis***

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DOI:10.34119/bjhrv7n3-390

Submitted: May 17th, 2024

Approved: Jun 07th, 2024

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ABSTRACT

Lemierre's syndrome (LS) stands as a rare and life-threatening condition. It is secondary to an acute oropharyngeal infection, leading to thrombosis of the internal jugular vein (IJV) and subsequent dissemination to other organs through metastatic septic emboli, predominantly affecting the lungs. While anaerobic bacterium such as *Fusobacterium necrophorum* typically prevail as etiological agents for this syndrome, the presented case illustrates an uncommon occurrence of Lemierre's Syndrome incited by a co-infection of *Staphylococcus aureus* and *Mycobacterium tuberculosis* in a 17-year old immunocompetent female. This highlights the importance of identifying alternative etiological agents capable of provoking this severe condition in order to provide tailored and timely therapeutic measures.

Keywords: Lemierre's syndrome, *Staphylococcus aureus*, *Mycobacterium tuberculosis*, oropharyngeal infections.

RESUMO

A síndrome de Lemierre é uma condição rara e potencialmente fatal, secundária a uma infecção orofaríngea aguda, que evolui com trombose de veia jugular interna (VJI) e consequente disseminação, através de êmbolos sépticos metastáticos, sendo o pulmão o principal sítio acometido. O quadro é causado, majoritariamente, por bactérias anaeróbicas. Este relato de caso descreve o quadro de uma paciente do sexo feminino, 17 anos de idade e imunocompetente, com diagnóstico de Síndrome de Lemierre causada pela coinfeção por *Staphylococcus aureus* e *Mycobacterium tuberculosis*, duas bactérias não usuais associados à doença. A identificação de outros agentes etiológicos capazes de gerar essa doença grave é de fundamental importância para ofertar tratamento oportuno e específico.

Palavras-chave: síndrome de Lemierre, *Staphylococcus aureus*, *Mycobacterium tuberculosis*, infecção orofaríngea.

RESUMEN

El síndrome de Lemierre es una afección rara y potencialmente mortal, secundaria a una infección orofaríngea aguda, que progresa a trombosis de la vena yugular interna (VYI) y consecuente diseminación a través de émbolos sépticos metastáticos, siendo el pulmón el principal sitio afectado. La afección es causada principalmente por bacterias anaeróbicas. Este reporte de caso describe la condición de una paciente femenina, de 17 años e inmunocompetente, diagnosticada con Síndrome de Lemierre causado por coinfección por *Staphylococcus aureus* y *Mycobacterium tuberculosis*, dos bacterias inusuales asociadas a la enfermedad. La identificación de otros agentes etiológicos capaces de generar esta grave enfermedad es de fundamental importancia para ofrecer un tratamiento oportuno y específico.

Palabras clave: síndrome de Lemierre, *Staphylococcus aureus*, *Mycobacterium tuberculosis*, infección orofaríngea.

1 INTRODUCTION

Lemierre's syndrome (LS) represents a rare and potentially life-threatening complication primarily affecting immunocompetent adolescents and young adults, as documented by Valerio *et al.* (2020a). The syndrome is distinguished by its association with recent acute oropharyngeal infections, leading to thrombosis of the internal jugular vein (IJV) and subsequent dissemination to other organs through metastatic septic emboli, as emphasized by Gore (2020).

While anaerobic bacterium *Fusobacterium necrophorum* stands as the predominant causative agent, identified in approximately one-third of cases, other pathogens such as *Streptococcus* and *Klebsiella* have also been implicated, as noted by Lee *et al.* (2020). Notably, *Staphylococcus aureus* has emerged as a plausible albeit infrequent etiological factor in LS over recent decades, characterized as a facultative anaerobic bacterium in these instances (Elkakeem *et al.*, 2020; Amarnani; Ranjan, 2022).

In the pre-antibiotic era, this infectious condition presented itself with a 90% mortality rate (Van Hoecke *et al.*, 2019), making early diagnosis and treatment critical. The main finding for suspicion of Lemierre's syndrome is thrombosis of the IJV, which is described in more than 80% of the cases and is rarely present in lymph node tuberculosis (Gore, 2020; Salami *et al.*, 2019).

Therefore, this case report presents an instance of Lemierre's syndrome secondary to co-infection by *S. aureus* and *Mycobacterium tuberculosis*, both of which are considered unusual causative agents for this condition.

2 CASE REPORT

A 17-year-old female presented with a variety of symptoms including odynophagia, myalgia, prostration, anorexia, and a 40°C fever persisting for a duration of two weeks. Clinical examination revealed bulging, erythema, and tenderness upon palpation of the left cervical region, alongside trismus, dysphagia, productive cough, and mild dyspnea. Despite initiating oral antibiotic therapy consisting of 500 mg amoxicillin tid for a week, symptomatology failed

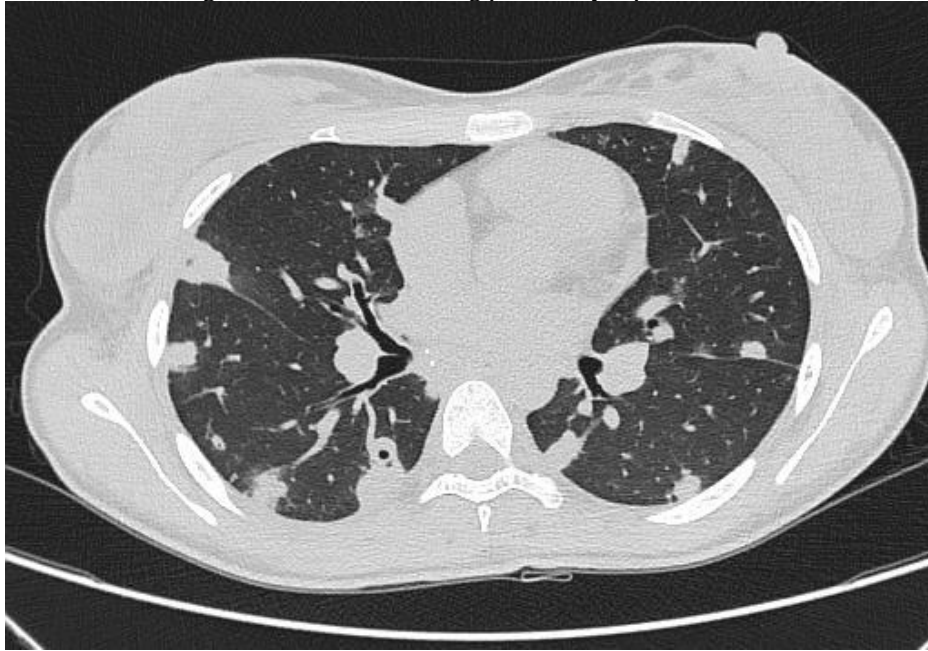
to ameliorate. Consequently, referral to a tertiary healthcare facility ensued due to sustained fever, exacerbated respiratory distress, and radiographic evidence from a chest X-ray demonstrating bilateral opacities, particularly affecting the apical pulmonary zones, at times exhibiting cavitation.

Upon admission to the tertiary center, the patient maintained a stable albeit compromised clinical status, characterized by a respiratory rate of 24 breaths per minute, a heart rate of 92 beats per minute, and a tendency toward hypotension (100 x 60 mmHg). Painful lymphadenopathy was noted upon examination, particularly evident in the left cervical and parotid regions. Laboratory investigations unveiled leukocytosis at 23.570 leukocytes/mm³ and an elevated C-reactive protein (CRP) level of 14.58 mg/dL. In response to these findings, empirical intravenous antimicrobial therapy was promptly initiated, comprising vancomycin 1g bd, in conjunction with piperacillin with tazobactam 4.5g qid.

Contrast-enhanced cervical spine computed tomography (CT) revealed densification of the myo-adipose planes, concomitant with the presence of fluid collections within the left parapharyngeal and parotid spaces. Additionally, notable findings included an increased number and enlarged size of cervical lymph nodes, alongside evidence of thrombosis affecting the left IJV. Subsequently, anticoagulation therapy commenced with subcutaneous enoxaparin at a dosage of 40 mg bd.

Further imaging via chest CT demonstrated the presence of multiple nodular opacities, exhibiting varying degrees of consolidation and cavitation, measuring up to 4.5 cm. These pulmonary findings were accompanied by thickening of the interlobular septa and ground-glass opacities, suggestive of pulmonary septic emboli (see Figure 1).

Figure 1. Chest CT showing pulmonary septic emboli.



Source: Prepared by the authors themselves.

Fibrobronchoscopy with bronchoalveolar lavage collection yielded a positive result on molecular rapid testing (MRT) for *Mycobacterium tuberculosis*, displaying susceptibility to rifampicin. Concurrently, blood cultures upon admission identified Methicillin-sensitive *Staphylococcus aureus* (MSSA), sensitive to clindamycin, linezolid, vancomycin, and gentamicin. Notably, a transesophageal echocardiogram did not reveal indicative signs of endocarditis.

In light of these findings, antibiotic therapy was adjusted to include moxifloxacin at a dosage of 400 mg qd and linezolid at 600 mg bd, due to their broad-spectrum coverage against both bacterial and mycobacterial pathogens. This therapeutic regimen was supplemented with treatment for both pulmonary and extrapulmonary tuberculosis according to the RHZE scheme, comprising 4 tablets qd containing 150 mg rifampicin, 75 mg isoniazid, 400 mg pyrazinamide, and 275 mg ethambutol.

However, subsequent hepatotoxicity emerged, as evidenced by elevated levels of aspartate transaminase (AST) from 21 U/L to 103 U/L and alanine transaminase (ALT) from 37 U/L to 124 U/L, necessitating the suspension of anti-tuberculosis treatment. Following the initiation of antibiotic therapy, notable clinical and laboratory improvements were observed. Once AST and ALT levels normalized, the RHZE regimen was reintroduced. The patient was discharged from the hospital with the RHZE regimen and prescribed rivaroxaban at a dosage of 20 mg qd, with scheduled outpatient follow-up.

3 DISCUSSION

LS stands as a rare and severe medical entity, estimated to afflict approximately 0.8 to 3.6 million cases per million individuals, as documented by Valerio *et al.* (2020a). The hallmark diagnostic triad encompasses the presence of a recent primary infection within the head or neck region, evidence of IJV thrombosis or metastatic septic emboli, and growth of anaerobic bacteria in blood cultures, as delineated by Tiwari (2023).

However, the necessity of the latter criterion remains debatable, given reports implicating alternative pathogens in LS pathogenesis, notably *Staphylococcus aureus*, detected in approximately 7% of cases, predominantly exhibiting methicillin resistance, as highlighted by Gore (2020). Despite cutaneous sites predominating as primary infection foci for this bacterium, nearly half of patients harbor nasal cavity colonization, posing a potential avenue for bacteremia, as elucidated by Elkakeem *et al.* (2020).

The presentation of LS precipitated by lymph node tuberculosis represents an exceedingly rare occurrence, documented in the literature through a solitary case report by Salami *et al.* (2019). Plausible explanations for IJV thrombosis encompass the thrombogenic attributes of the *Mycobacterium tuberculosis*, coupled with mechanical vascular obstruction facilitated by local lymphadenopathy or contiguous lymphatic infection dissemination.

Conversely, infection attributable to *Mycobacterium tuberculosis*, particularly in its extrapulmonary guise, tends to manifest more frequently among immunocompromised individuals. This dynamic potentially elucidates the observed coinfection exacerbated by *S. aureus*, rendering the reported case notably intriguing, given the immunocompetent status of the patient, as posited by Salami *et al.* (2019).

Most hospitalized LS cases manifest with severe sepsis or metastatic septic lesions in target organs, with pulmonary abscess formation predominating due to the initially subtle symptoms associated with acute oropharyngeal infection, which subsequently progresses to invade the parapharyngeal space, culminating in IJV thrombosis, as underscored by Pinheiro *et al.* (2014). The presence of protrusion, erythema, and tenderness upon cervical palpation heightens suspicion of disease progression into adjacent tissues.

Contrast-enhanced CT emerges as the modality of choice for LS investigation, serving as the gold standard for diagnosing IJV thrombosis and evaluating associated complications such as pulmonary septic emboli. Doppler ultrasound serves as a rapid, cost-effective, and non-invasive alternative for identifying IJV thrombosis, as acknowledged by Amarnani (2022).

Antibiotic therapy constitutes a cornerstone in mitigating LS mortality risk, typically

administered over a duration of 4 to 6 weeks. Treatment regimens commonly encompass beta-lactams or carbapenems in conjunction with metronidazole, given the predominance of anaerobic agents. However, multifaceted antibiotic administration is frequently warranted throughout the disease course, as outlined by Lee *et al.* (2020). Surgical intervention often becomes imperative due to the potentially fatal sequelae associated with septic emboli, as emphasized by Valerio *et al.* (2020b).

The topic of anticoagulation in LS remains contentious, given thrombosis's secondary nature to the infectious process, with limited evidence supporting significant vessel recanalization following anticoagulant administration. Moreover, concerns regarding heightened bleeding risk and potential septic emboli dissemination further complicate this therapeutic consideration, as discussed by Adedeji *et al.* (2020) and Gore (2020). Nonetheless, anticoagulation strategies are deemed appropriate for hospitalized LS patients at heightened risk of new thrombotic events, particularly intracranial occurrences, even subsequent to antibiotic initiation, as underscored by Valerio *et al.* (2020b) and Tiwari (2023).

4 CONCLUSION

LS stemming from oropharyngeal infection constitutes a life-threatening complication, underscoring the criticality of prompt diagnosis and intervention to mitigate the heightened risk of mortality and long-term neurological sequelae. Consequently, maintaining a high index of clinical suspicion is paramount, with thrombosis of the internal jugular vein serving as the hallmark feature of the disease.

While the majority of LS cases are attributed to anaerobic bacterial pathogens, the presented case report illuminates a rare occurrence wherein LS arises from *Mycobacterium tuberculosis* infection, concomitant with co-infection by *Staphylococcus aureus*. This underscores the significance of identifying alternative etiological agents capable of inciting this grave syndrome to facilitate the provision of tailored and timely therapeutic measures.

Moreover, elucidating the diverse microbial landscape contributing to LS pathogenesis is indispensable for refining diagnostic protocols and optimizing treatment strategies, thereby enhancing clinical outcomes and mitigating the morbidity and mortality associated with this formidable condition.

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