DOI：10.6314/JIMT.202304_34(2).07 內科學誌 2023：34：124-129

Lemierre's Syndrome, an Easily-Misdiagnosed but Fatal Infectious Disease: A Case Report

Hsiang-ling Lin, Chang-Pan Liu

Division of Infectious Diseases, Department of Internal Medicine, MacKay Memorial Hospital, Taipei, Taiwan

Abstract

Lemierre's syndrome usually developes after an episode of acute upper respiratory infection. Fever, sore throat and neck pain are not specific symptoms and are usually treated as acute pharyngitis or tonsillitis. However, septic thrombophlebitis of the internal jugular vein with septic emboli that cause metastatic infections may make this disease complicated and fatal. We present a 28-year-old man who was initially diagnosed with acute tonsillitis and suspect EBV infection. After further evaluations, he was finally diagnosed with Lemierre's syndrome and was treated successfully.

Key Words: Acute tonsillitis, *Fusobacterium necrophorum*, Internal jugular vein septic thrombophlebitis, Infectious mononucleosis, Lemierre's syndrome, Metastatic infections

Introduction

Lemierre's syndrome, also known as postanginal septicaemia, is a disease that mostly developes after an episode of upper respiratory or oropharyngeal infection.[1]

It is characterized by septic thrombophlebitis of the internal jugular vein with septic emboli and metastatic infections, including pneumonia, empyema, septic arthritis, soft tissue infection, abscess formation or osteomyelitis.[2]

This disease is particularly pertinent among young populations, and early awareness of this disease and adequate antibiotic treatment are important.[3]

Case report

This is a 28-year-old man without known systemic disease. He works as a waiter in a sushi restaurant. He presented with intermittent fever for 2 days, accompanied by sore throat, general malaise and poor appetite.

The reported no productive cough, rhinorrhea, skin rash or eschar, headache, abdominal pain, diarrhea, urinary symptoms or flank pain.

He traveled to Tainan and had a picnic on a grassland one week before these symptoms developed, but he denied similar symptoms in his family members and friends. Thus, he was brought to the emergency room (ER).

Reprint requests and correspondence：Dr. Hsiang-ling, Lin, M.D.
Address：Division of Infectious Diseases, Department of Internal Medicine, MacKay Memorial Hospital, No. 92, Sec. 2, Zhongshan N. Road, Taipei, Taiwan.

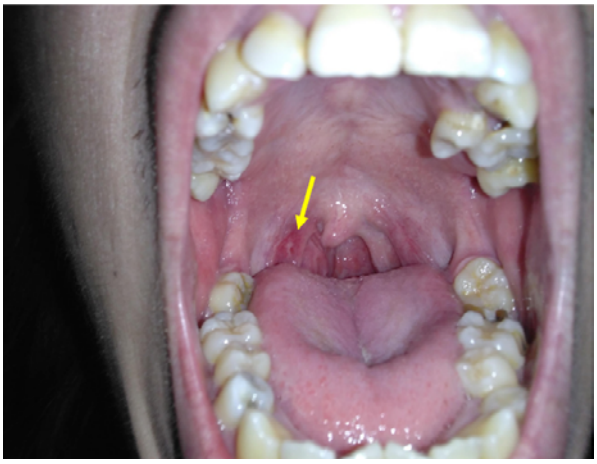

Figure 1. Enlarged and exudative tonsil on the right side

On physical examination, he presented with an enlarged and exudative tonsil on the right side (Figure 1), and mild right neck swelling. The chest x-ray showed no obvious pneumonia patch or pleural effusion. The laboratory data showed leukocytosis with thrombocytopenia, liver enzymes abnormalities and raised C-reactive protein (CRP). (Table 1)

He was admitted under the impression of acute tonsillitis with reactive neck lymphadenopathy and suspect EBV infection. Empiric antibiotics treatment with Flomoxef and doxycycline for scrub typhus (fever, increased liver enzymes and history of picnicking on the grassland) was administered.

Abdominal echography showed mild splenomegaly and mild ascites and no gallbladder wall thickness or biliary tract obstruction; this supported the diagnosis hepatitis. However, the serology of mycoplasma antigen and antibody and the Epstein-Barr virus (EBV) and cytomegalovirus (CMV) titers showed no active infection. (Table 1)

His fever persisted under antibiotic treatment

Table 1. Blood and biochemistry tests in the emergency room

		Value	Reference range
White cell count	10^3/uL	14.8	13-18
Band	%	4	0-6
Neutrophil	%	69	55-75
Monocyte	%	21	0-10
Lymphocyte	%	4	20-40
Platelet	10^3/uL	51	140-450
Aspartate amino transferase (AST)	IU/L	45	15-41
Alanine amino transferase(ALT)	IU/L	55	14-40
Total bilirubin	mg/dL	2.3	0.3-1.2
Direct bilirubin	mg/dL	0.8	0.1-0.5
Blood urea nitrogen	mg/dL	16	8-20
Creatinine	mg/dL	1.2	0.4-1.2
C-reactive protein	mg/dL	21.416	0-0.79
EB VCA IgM EB VCA IgG EBV EA IgG EBV NA IgG	U/mL	<10 137 <5 >600	<36(-),>44(+) <18(-),>22(+) <9(-),>11(+) <18(-),>22(+)
CMV IgG CMV IgM	IU/mL COI	172.00 0.152	<0.5(-),≥1.0(+) <0.7(-),≥1.0(+)
M. pneumoniae IgG Ab *M. pneumoniae IgM Ab*	AU/mL Index	<0.1 5.2	<10.0(-),≥10.0(+) <10.0(-),≥10.0(+)

after admission for three days. Worsen sore throat with right neck swelling, productive cough and mild shortness of breath were observed. Blood cultures taken at the ER reported gram-negative bacilli; thus, we escalated antibiotic regimen to doripenem.

A computed tomography (CT) scan for deep neck infection was performed and showed right tonsil swelling, with lymphadenopathy and septic thrombophlebitis of the right internal jugular vein (Figure 2). In addition, follow-up chest X-ray showed right pneumonia with pleural effusions (Figure 3).

The final blood culture reports revealed *Fusobacterium necrophorum* for two sets. He was diagnosed with Lemierre's syndrome. (*F. necrophorum* bacteremia, internal jugular vein septic thrombophlebitis, metastatic infections with pneumonia and pleural effusions)

We consulted a dentist to consider bacteremia from an odontogenic infection, and there were dental caries and chronic periodontitis. There were

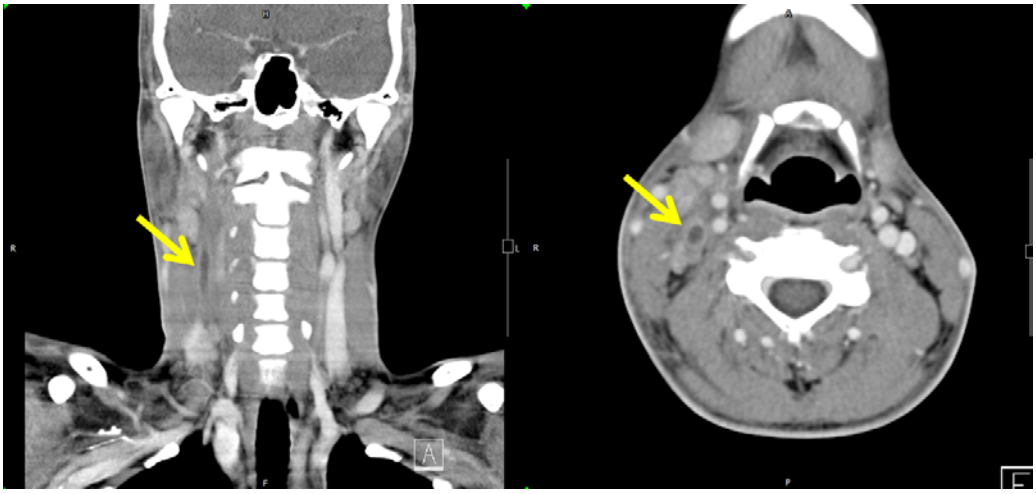

Figure 2. Right tonsil swelling, with lymphadenopathy and septic thrombophlebitis of the right internal jugular vein

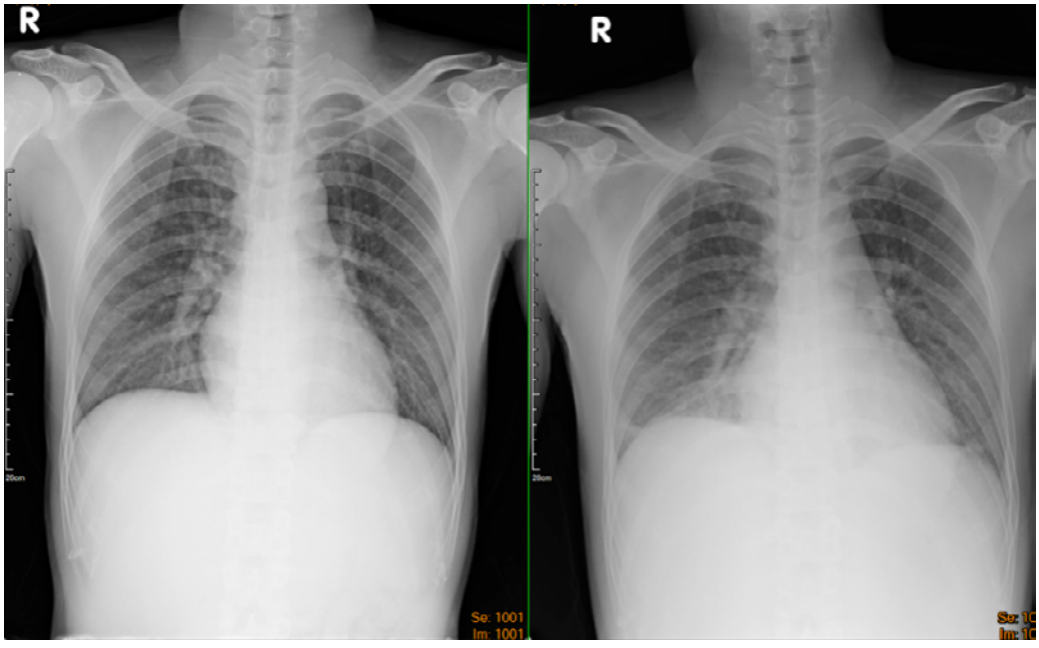

Figure 3. Right pneumonia with pleural effusion developed

residual roots, and he underwent tooth extraction. Heart sonography reported no obvious vegetation.

When his fever subsided, we de-escalated the antibiotic regimen to ceftriaxone and metronidazole, and followed up with two sets of blood cultures.

The patient's clinical symptoms improved, and the right neck mass subsided. The patient reported that his sore throat, productive cough, shortness of breath and neck pain had resolved. The follow-up blood cultures showed no growth in five days for two sets. After three weeks of antibiotic treatment, he was discharged and followed up at the outpatient department.

Discussion

Lemierre's syndrome was first reported in 1936 by a French doctor, Andre Lemierre.

The most common initial cause is a tonsillar or a peri-tonsillar abscess. The original work of E. Frankel in the 1919 German authorities considered these cases of septicemia to be result of thrombophlebitis of the tonsillar and peritonsillar veins, which can spread to the internal jugular vein or even to the facial vein.[1]

Fusobacterium necrophorum is the most common causative pathogen of Lemierre's syndrome, followed by anaerobic streptococci, staphylococci and *Klebsiella pneumoniae*.[2-3]*F. necrophorum* is an anaerobic, gram-negative bacillus bacteria commonly found in the oropharynx, gastrointestinal tract and female genital tract.[3-4]

A meta-analysis study reported the association between *F. necrophorum* and acute sore throat in primary healthcare, although the association is weaker than that with group A streptococcus.[5] Another study revealed a higher prevalence of *F. necrophorum* in the throat swab cultures from patients with acute tonsillitis, which is compatible to the result that Lemierre's syndrome usually developed after an episode of upper respiratory infection, especially in acute tonsillitis.[2]

Lemierre's syndrome is also reported to be associated with infectious mononucleosis and EBV infection. Decreased secretion of immunoglobulin on the tonsil surface under infectious mononucleosis results in increased bacterial colonization, and easy infection has been purposed for possible mechenism.[4,6] A retrospective analysis study by Chacko, E M et al. suggested that EBV-related pharyngitis makes the environment favorable for *F. necrophorum* growth.[7]

The incidence of Lemierre's syndrome is higher in younger generations, with the incidence between 0.6 and 2.3 per million population.[8] A 3-year prospective study in Demark reviewed 58 cases of Lemierre's syndrome in young people aged 15-24 years. [9] Coincidentally, another systemic review 137 cases of Lemierre's syndrome reported that patients aged 15-30 years have a higher incidence rate. [10]

A systemic review study by Karkos PD et al. reported that the male to female ratio was 1:1[11], while other studies suggest that Lemierre's syndrome might occur more often in men.[12-13]

Regarding the pathogenesis, it has been thought that the pharyngeal mucosa is weakened by viral or bacterial infections, resulting in the causative bacteria invading the internal jugular vein.[14] Fusobacterial lipopolysaccharide endotoxin may induce platelet aggregation and lead to thrombus formation.[4]

By septic thrombophlebitis and septic emboli formation, metastatic infections may develope. Pneumonia and pleural empyema are the most common metastatic infections in Lemierre's syndrome.[3] In addition, septic arthritis, retroperitoneum necrotizing fasciitis, soft tissue abscess, emphysematous osteomyelitis, and even severe sepsis with multiple organ failure have also been reported. [15]

In the case we presented, the patient first presented with fever, sore throat with neck swelling and acute hepatitis, leading to the impression of EBV

infection. However, the fever persisted and right neck swelling developed. Blood cultures yield *F. necrophorum*, which is the most commonly isolated pathogen in this syndrome.[3]

Regarding antibiotic treatment for Lemierre's syndrome, adequate coverage for *Fusobacterium* and some oral streptococci is necessary. Because *F. necrophorum* is intrinsically resistant to macrolides, fluoroquinolones, tetracyclines, and aminoglycosides.[16] β-lactam antibiotics with anaerobic activity, such as piperacillin-tazobactam, metronidazole, and clindamycin are good choices. Antimicrobial therapy should continue for 3 to 6 weeks by case.[17] One review paper by Osowicki, Joshua et al. suggests metronidazole as the best, because it is bactericidal and shows good penetrations into tissues and cerebrospinal fluid.[18]

The role of anticoagulation in treatment remains uncertain. There are no trials or studies focusing on evaluating anticoagulant use in Lemierre's syndrome. However, a meta-analysis published in 2020 by Mitchell R Gore reviewed 427 studies and did not find significant effects in patients treated with anticoagulation for Lemierre's syndrome.[19]

Our patient was initially started on Flomoxef under the impression of acute tonsillitis and hepatits. The antibiotic regimen escalated to doripenem due to persistent fever, and blood cultures reported *F. necrophorum* bacteremia; then, the antibiotics were de-escalated to ceftriaxone and metronidazole when the fever subsided. He did not receive any anticoagulation therapy during the whole course. The patient was discharged after a complete antibiotic treatment course for bacteremia and when there was no growth in the repeat blood cultures.

Lemierre's syndrome may be easily-misdiagnosed because its initial presentation with fever, sore throat and neck pain is nonspecific and could mimic other common diseases. A review article suggested clinicians to be alert to patients with prolonged or worsening symptoms of pharyngitis, patients with a second site of infection, such as pneumonia or septic arthritis, and patients with soft tissue infection in the neck.[20]

We report this case to raise awareness of Lemierre's syndrome among young patients. When Lemierre's syndrome is suspected, appropriate antibiotic treatment should not be delayed.

References

1. Lemierre A. On certain septicæmias due to anaerobic organisms. Lancet 1936; 227(5874):701-3.
2. Jensen A, Hansen TM, Bank S, Kristensen LH, Prag J. *Fusobacterium necrophorum* tonsillitis: An important cause of tonsillitis in adolescents and young adults. Clin Microbiol Infect 2015;21(3):266.e1-3.
3. Lee WS, Jean SS, Chen FL, et al. Lemierre's syndrome: A forgotten and re-emerging infection. J Microbiol Immunol Infect 2020;53(4):513-7.
4. Riordan T. Human infection with *Fusobacterium necrophorum* (Necrobacillosis), with a focus on Lemierre's syndrome. Clin Microbiol Rev 2007;20(4):622-59.
5. Dalen CT, Mekhail AM. Lemierre syndrome: Early recognition and management. CMAJ 2015;187(16):1229-31.
6. Stenfors LE, Räisänen S. Immunoglobulin-coated bacteria on the tonsillar surface during infectious mononucleosis. J Laryngol Otol 1996;110(4):339-42.
7. Chacko EM, Krilov LR, Patten W, Lee PJ. Lemierre's and Lemierre's-like syndromes in association with infectious mononucleosis. J Laryngol Otol 2010;124(12):1257-62.
8. Syed MI, Baring D, Addidle M, Murray C, Adams C. Lemierre syndrome: Two cases and a review. Laryngoscope 2007;117(9):1605-10.
9. Hagelskjaer Kristensen L, Prag J. Lemierre's syndrome and other disseminated *Fusobacterium necrophorum* infections in Denmark: A prospective epidemiological and clinical survey. Eur J Clin Microbiol Infect Dis 2008;27(9):779-89.
10. Johannesen KM, Bodtger U. Lemierre's syndrome: current perspectives on diagnosis and management. Infect Drug Resist 2016;9:221-7.
11. Karkos PD, Asrani S, Karkos CD, et al. Lemierre's syndrome: A systematic review. Laryngoscope 2009;119(8):1552-9.
12. Brazier JS, Hall V, Yusuf E, et al. *Fusobacterium necrophorum* infections in England and Wales 1990-2000. J Med Microbiol 2002;51(3):269-72.
13. Hagelskjaer LH, Prag J, Malczynski J, et al. Incidence and clinical epidemiology of necrobacillosis, including Lemierre's syndrome, in Denmark 1990-1995. Eur J Clin Microbiol Infect Dis 1998;17(8):561-5.
14. Chirinos JA, Lichtstein DM, Garcia J, Tamariz LJ. The evolution of Lemierre syndrome: Report of 2 cases and review of the literature. Medicine (Baltimore) 2002;81(6):458-65.
15. Amin R, Fretz T, Harmon C, Vali K. Lemierre's syndrome: A rare cause of multifocal infection in an adolescent. J Pediatr Surg Case Rep 2022;84:102350.

16. Recchia A, Cascella M, Altamura S, et al. Early diagnosis and antibiotic treatment combined with multicomponent hemodynamic support for addressing a severe case of Lemierre's Syndrome. Antibiotics (Basel) 2021;10(12):1526.
17. Appelbaum PC, Spangler SK, Jacobs MR. Beta-lactamase production and susceptibilities to amoxicillin, amoxicillin-clavulanate, ticarcillin, ticarcillin-clavulanate, cefoxitin, imipenem, and metronidazole of 320 non-Bacteroides fragilis Bacteroides isolates and 129 fusobacteria from 28 U.S. centers. Antimicrob Agents Chemother 1990;34(8):1546-50.
18. Osowicki J, Kapur S, Phuong LK, Dobson S. The long shadow of lemierre's syndrome. J Infect 2017;74 Suppl 1:S47-53.
19. Gore MR. Lemierre Syndrome: A meta-analysis. Int Arch Otorhinolaryngol 2020;24(3):e379-85.
20. Carius BM, Koyfman A, Long B. High risk and low prevalence diseases: Lemierre's syndrome. Am J Emerg Med 2022;61:98-104.

雷米爾氏症，少見卻可能致命的感染症：病例報告

林湘玲　劉昌邦

台北馬偕紀念醫院　內科部感染科

摘　要

雷米爾氏症通常伴隨上呼吸道感染後發生。發燒、喉嚨及脖子疼痛容易被誤判為急性咽喉炎或扁桃腺炎，但感染性靜脈炎伴隨敗血性血栓造成全身各系統的轉移感染有可能發生，會轉變成致命且棘手的感染症。我們報告一位28歲年輕男性一開始被診斷為急性扁桃腺炎並懷疑EB病毒感染，但隨後影像學表現及細菌學培養結果被診斷為雷米爾氏症。希望我們的診斷與治療經驗能提供各位臨床醫師參考。