Case Report of Leimier's syndrome associated with Fusobacterium nucleatum infection without internal Jugular venous thrombus

Haidang Nguyen[1], Lakshmi Uppaluri[1], Jay Sangani [1], Mitchell Simon[2], Patricia Whitleywilliams [1], and Aisha Baig[3]

[1]Rutgers The State University of New Jersey
[2]Rutgers Robert Wood Johnson Medical School New Brunswick
[3]Rutgers University

March 07, 2024

Abstract

Fusobacterium nucleatum is an anaerobe that is commensal to the human oral cavity. It is usually a component of periodontal plaque that is emerging as a pathogen and quickly attracting attention of the medical and research communities. It has been even discovered in bronchoalveolar lavage of some patients with lung cancer. 24, 25 Lemierre's syndrome (LS) is characterized as septic thrombophlebitis of the internal jugular vein, which usually begins with oropharyngeal infection that worsens and lead to inflammation of the wall of the jugular vein9 . This is the hallmark of the disease. However, in this case, there was no thrombophlebitis of the internal jugular vein. There is one other case presentation where it was diagnosed without the internal jugular vein involvement.22. Most sequelae involve infected thrombus of the vein, soft tissue inflammation, persistent bacteremia, and septic emboli, often leading to frequent metastatic infections14,3. Interestingly enough, in the age of SARS-CoV-2, LS has also been mistaken for multisystem inflammatory syndrome in children (MIS-C)23. We present a previously healthy 20-year-old female college student, who tested positive to COVID-19 capsid antibody, transferred from her local hospital to Bristol Meyer's Squib Children's hospital (BMSCH) for suspected LS with loculated infected pleural effusions and necrotizing pneumonia with lung abscess secondary to Fusobacterium nucleatum, systemic and emphysematous osteomyelitis possibly secondary to septic emboli, thrombocytopenia, and palatine tonsil and thyroid abscess.

1. Introduction

Fusobacterium nucleatum was first reported as an anaerobic oral commensal and a periodontal pathogen associated with multiple human diseases, described for the first time in early 1900's[17]. The pathogen has five proposed subspecies (ss):*animalis, ss fusiforme, ss nucleatum, ss polymorphum, and ss vincentii* [15] and often present in small numbers as part of the normal human throat flora[15,10].

LS is a rare disease that presents in healthy young adults without any underlying medical conditions[8]. LS is highly curable if appropriate antibiotic therapy is administered on a timely basis. In the pre-antibiotic era, LS was a common complication of pharyngitis with poor prognosis, resulting in 90%-100% mortality.[28]Although the prompt use of β-lactam antibiotics have reduced the incidence to 0.8 to 1.5 cases per million persons per year, LS still remains a potentially life-threatening disease that results in a 15% mortality rate.[8, 16, 29] A study in Denmark revealed the annual incidence of 14.4 cases per million people among young adults aged 14-24 years old[11]. Lastly, surgical drainage of abscesses is indicated for patients who fail to respond successfully to antibiotics alone[27]. Although using anticoagulation in LS is common, it remains controversial.

Moreover, it is important for physicians to include LS in their differentials for patients presenting with toxic appearance, fever, sore throat, respiratory distress and cough to ensure timely diagnosis of this potentially life-threatening disease and start appropriate microbiological therapy[2].

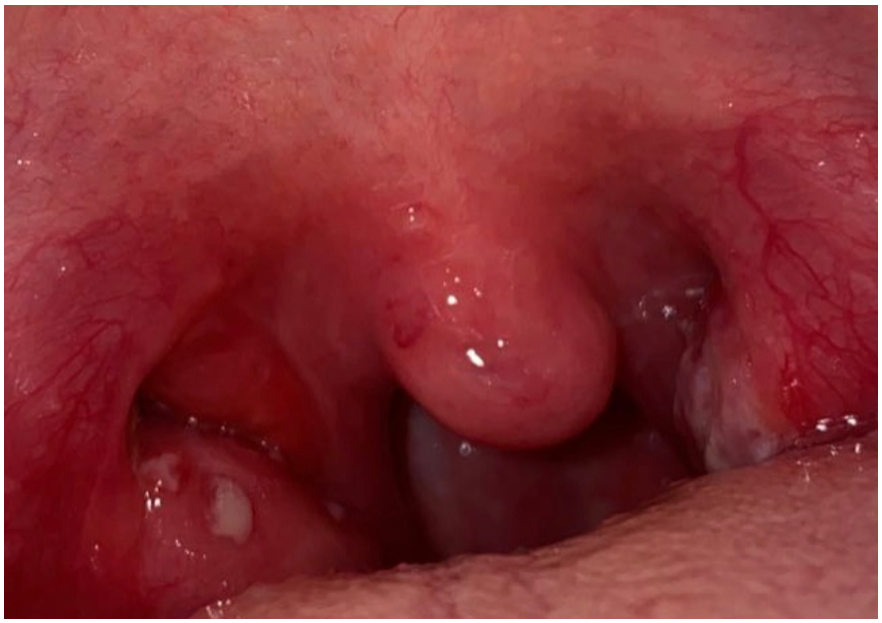
2. Clinical Case

Patient is a 20-year-old female patient who initially presented with pharyngitis and was evaluated via telemedicine by her physician who prescribed 5- day course of azithromycin for presumed beta hemolytic streptococcal pharyngitis due to exposure to person who tested positive for rapid group A beta hemolytic streptococcus and Epstein-Barr virus.

She was initially studying at home and traveled to Florida during her spring break to visit her college friends. She slept on a sofa in a college dormitory for the week and shared utensils. One of her friends tested positive for COVID-19 PCR about three months ago.

Due to persistence of sore throat, fever, chills and lymphadenopathy she came to the Emergency Room (ER) of her local hospital 1 day prior to admission.

Additionally, her mother works in at an elderly center and routinely tested negative for COVID-19 biweekly. No other family members were sick.



(Figure 1) Exudative pharyngitis is demonstrated 13 days prior to BMSCH admission

Due to continued and increased severity of sickness, she arrived to the ER at her local hospital due to continued fevers, new onset of cough, swollen glands, worsening sore throat, shortness of breath, increased work of breathing, new rash on her left wrist, scleral icterus, and blurry vision characterized by enhanced brightness. This was 12 days after her arrival to her hometown. Her ER vitals include temperature 98.4 °F, O_2 saturation 93% room air, blood pressure 98/67, respiratory rate 40 breaths per minute, and tachycardia at 116 beats per minute. Physical exam was pertinent for decreased breath sounds at bases bilaterally on lung exam, erythema of posterior pharynx with mild exudate present (as in figure 1), mild anterior cervical lymphadenopathy and tenderness of neck, and diffuse mild tenderness on abdominal palpation.

There were four COVID PCR tests reported as negative. Imaging included chest x-ray and CT scan of the chest, which showed bilateral cavitary pneumonia with left pleural effusion. Her blood work included blood culture, CBC with WBC of 3.9 thousand/ul, absolute neutrophil count of >2000 thousand/ul, C-reactive protein 30.75 mg/dL, ferritin >1600 ng/mL, and procalcitonin 100 ng/ml. Other studies were negative for pulmonary embolism on CTA, HIV, urine legionella, urine streptococcus antigen, CMV, EBV IgM (positive

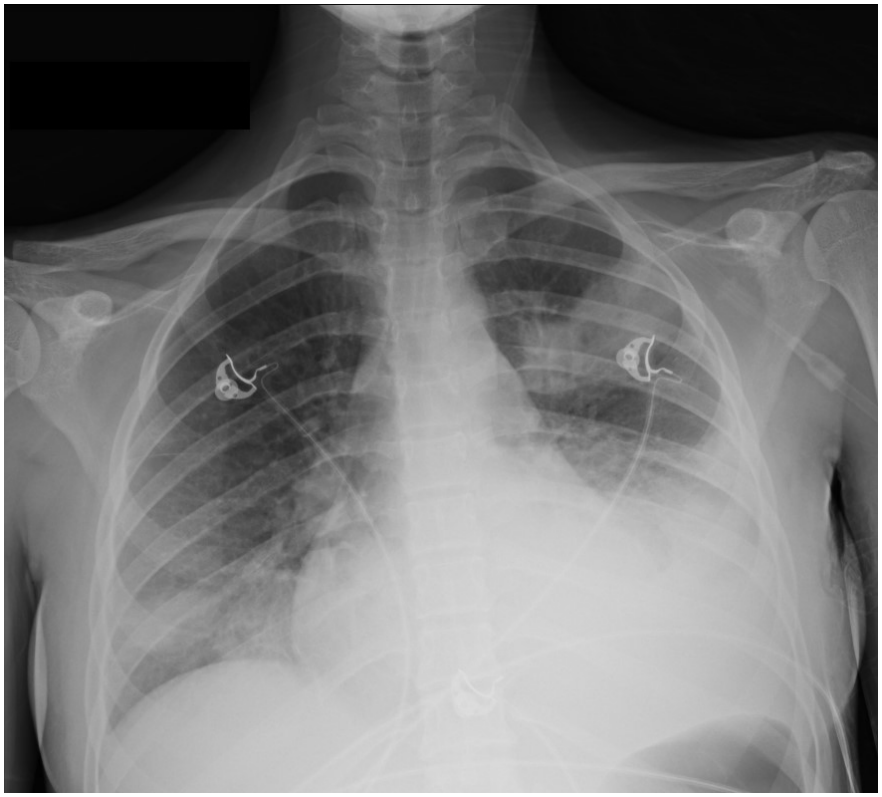
for IgG), throat culture, acid-fast bacillus, mycoplasma pneumonia IgM by IFA, and Rocky mountain spotted fever.

Laboratory reports at the hospital revealed blood culture positive for anaerobic gram-negative rods identified as *Fusobacterium nucleatum* . Due to significant drop in platelets at 11,000; she received plasma and platelet transfusion.

During this time period, she developed left wrist pain that gradually migrated to entire left hand and arm, improved, but then migrated to left shoulder causing limited mobility.

Her treatment at this hospital includes doxycycline and ceftriaxone, followed by left pleurocentesis, which removed 950 mL pleural fluid. Pleural fluid showed LDH 2,786 IU/L, glucose <5 mg/dL, and protein 1.5 g/dL, suggestive of an exudative pleural effusion. Surgical pathology report was impressive for left pleura-fibrinopurulent exudate, and cytology for pleural fluid was negative for malignancy.

Due to concerns of impending septic shock and worsening respiratory distress, she was then transferred to BMSCH after 1 day at former hospital for further evaluation and management. Multiple specialists including Pediatric Infectious Disease, Pediatric Surgery, Pediatric Ear Nose and Throat, Orthopedics, and Pediatric Pulmonary were consulted throughout hospital course.



(Figure 2) Image A is a plain film radiograph of the chest, which demonstrates a left sided pleural effusion (red arrow). Additionally, there are multiple airspace opacities (blue arrows) including cavitation in the left upper lobe. These findings are concerning for multifocal pneumonia with pleural effusion and cavitary necrosis. Images B (axial) and C (coronal) are CT scans of the neck with intravenous contrast which demonstrate enlargement of the right palatine tonsil with area of low attenuation centrally with mild peripheral rim enhancement with foci of air (green arrow). This represents a tonsillar abscess.

At the BMSCH, she was transferred to the pediatric intensive care unit immediately. Her PICU admission

vitals were temperature 99.0 °F, pulse 100 bpm, BP 111/55, RR 31 bpm, SpO_2 95% on room air. Physical exam showed pertinent findings of mild acute distress, tachypnea, rashes along ulnar side of L hand, dressing along L upper lateral thoracic region s/p thoracentesis, diminished breath sounds along bases bilaterally with no wheezing, crackles, or rhonchi, and suprasternal retractions present bilaterally.

Her further evaluation and management included almost daily imaging which included almost daily chest radiographs and CT scan of the chest which showed bilateral multifocal, necrotizing pneumonia characterized by pleural effusions with loculations, cavitary abscess, left empyema, and mediastinal lymphadenopathy (figure 3). Her initial admission CXR to BMSCH showed worsening multifocal pneumonia compared to outside hospital CXR.

Due to significant hypoxemia, she was initially on high-flow nasal cannula 20L at FiO2 30% but was changed to synchronized intermittent mandatory ventilation (SIMV). Due to septic shock, she required inotropes. Her antibiotic regime included cefepime and vancomycin. A CT scan of her chest including the neck on day 3 at BMSCH revealed right palatine tonsil and thyroid abscesses. Otolaryngology evaluated her with no recommendations to drain the thyroid abscess.

For further management of her pneumonia, she underwent video-assisted bilateral thoracoscopic surgery (VATS) along with insertion of bilateral chest tubes for pleural effusion, lung abscess, and empyema. After drainage of significant amount of fluid, she was weaned to HFLNC to maintain oxygen saturations above 92%.

Of note, all three blood cultures including anaerobic cultures of pleural fluid during her stay in the PICU was unremarkable. She was administered an 11-day course of vancomycin, and 28-day course of cefepime and metronidazole for anerobic coverage. The patient's pleural fluid also showed cell count within normal limits, elevated RBC count 46,906 #/cubic mm, and total nucleated cells BF 6,156 #/cubic mm. Her polysegmented neutrophils were 81%, lymphocyte 8%, monocyte 4%, and histiocyte 7%.

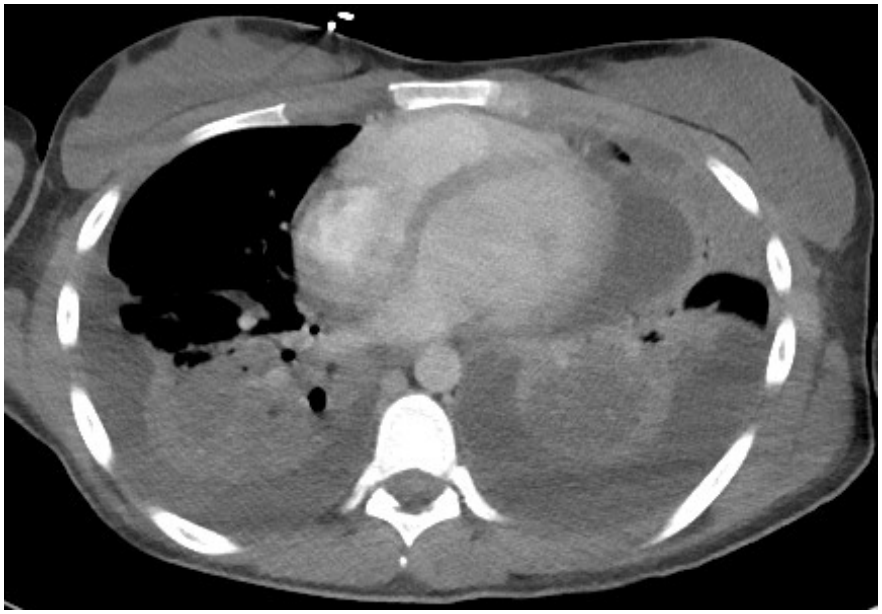
Slowly, her labs showed improvement: procalcitonin and C-reactive protein initially elevated at 98.01 ng/mL and 46.12 mg/dL, respectively, ultimately trended down to 0.33 ng/mL and 4.32 mg/dL 27 days later.

Patient's hemodynamic stability improved with chest tube draining after three TPA flushes into the left lung area of complex loculations, and continued antibiotics. Her chest tubes continued to drain her pleural fluid. Her right chest tube was then removed after draining a total of 422 mL. When her blood culture on admission was identified as*Fusobacterium nucleatum* on day 6 at BMSCH, her antibiotic coverage was altered to ceftriaxone, and metronidazole was continued. Patient was then transferred to hospital floor on 1liter nasal cannula. Her 24 French chest tube became clogged after draining a total of 4,020 mL, and a second 8 French pigtail catheter was inserted posterolaterally on her left side that drained an additional 3,260 mL in 7 days. Total fluid drained and recorded from all three tubes during her hospital course was 7,702 mL.

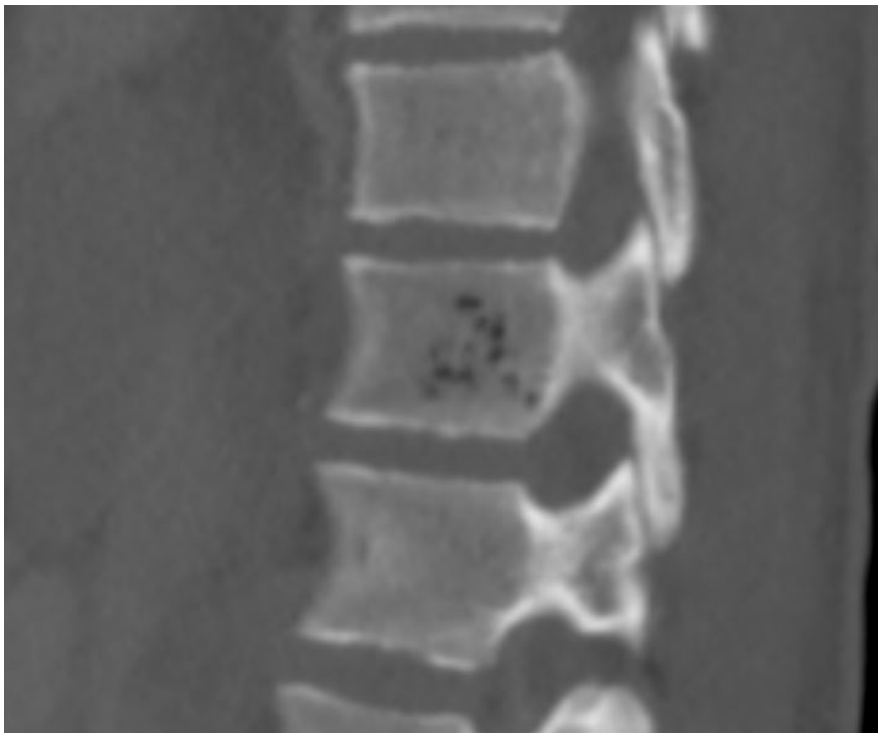
Due to concerns for any cardiac vegetation, echocardiogram showed tissue near tricuspid valve, small pericardial effusion, and no vegetations. Initial echocardiogram in the PICU showed fractional shortening of 38.5%, LVIDd of 5.6 cm, and LVIDs of 3.5 cm, which approximates an ejection fraction of 63% using the Teichholz formula.

Our patient needed prolonged hospitalization for continued fevers and oxygen dependence. Due to back pain localized at the left scapular area, further imaging, including MR studies of left upper extremity revealed musculoskeletal edema and proximal humeral osteomyelitis and T12 vertebral body emphysematous osteomyelitis (figure 4), which was an incidental finding.

Her bilateral duplex venous ultrasounds of the upper extremities and bilateral neck showed no thromboses, and duplex ultrasound of the carotids bilaterally was unremarkable, which is quite different from the other cases of LS.



(Figure 3) Image A is an axial CT scan of the chest with intravenous contrast, which demonstrates bilateral pleural effusions (blue arrows) and bilateral pulmonary consolidations (purple arrows). Image B is an ultrasound of the chest, which shows bilateral hypoechoic pleural effusions with thick septations (red arrow) consistent with empyemas. Image C is a coronal CT of the chest with intravenous contrast shows a cavitary left upper lobe mass (green arrow) concerning for cavitary/necrotizing pneumonia.



(Figure 4) Images A and B are sagittal CT scans of the spine in bone and lung windows which show foci of

dark low attenuation (red arrow) within the T12 vertebral body, which are suspected to be air within the vertebral body and represent emphysematous osteomyelitis by a gas forming organism. Follow up MRI of the thoracic spine is shown. The T12 vertebral body has high signal intensity on T2 weighted imaging (not shown). Images C and D are sagittal images pre and post contrast T1 weighted images. There is heterogenous enhancement (blue arrow) of the vertebral body without significant enhancement of the adjacent disc spaces, consistent with osteomyelitis. There is an associated tiny epidural abscess.

3. Discussion

Our case presents a complicated patient with Lemierre Syndrome with septic shock secondary to *Fusobacterium nucleatum* with most sequelae involving osteomyelitis, multi-organ abscesses, pericardial effusion, and bilateral pleural effusions secondary to bilateral necrotizing pneumonia (left>right) with lung abscesses. Although the patient presented with presumed streptococcal pharyngitis due to exposure to college friends, it is imperative to swab and test patient before antibiotic administration. As the patient returned with continued fevers and worsening of symptoms, the suspicion for Lemierre's syndrome is reasonable given patient's age group and deteriorating respiratory status. However, it is not unreasonable to be suspicious for multisystem inflammatory syndrome in children (MIS-C) as well considering the era of SARS-CoV-2 [23]. Serologic inflammatory markers also make LS highly likely[20]. Of note, LS can also present as sinusitis or mastoiditis in young adults, and approximately 75% of patients are male. Those affected are young individuals who are usually immunocompetent without serious comorbidity[1]. The patient's thromboembolic complications were not identified on any imaging studies; however, improvement with antibiotics, thoracentesis, VATS, and pleural fluid drained by chest tubes indicate that the etiology of medical condition to be suspicious for LS.

Due to *Fusobacterium nucleatum'* s ubiquitous nature as normal flora in many healthy individuals' oropharyngeal, gastrointestinal, and genitourinary tracts, it is imperative to obtain a history of the patient's onset of symptoms. Our patient traveled to another state to visit friends, attended several social events, and shared utensils with multiple persons. Furthermore, the patient had dental work done approximately two months prior to onset of symptoms. With the initial onset of pharyngitis after her trip in the context of dental work and cleaning, patient may demonstrate weakened host mucosal barriers, allowing commensal organisms such as *Fusobacterium nucleatum* to disseminate into her bloodstream. Reported risk factors for*Fusobacterium* bacteremia include immunosuppression, alcohol abuse, malignancy, older age, dialysis, and hospital acquired[21]. Moreover, *Fusobacterium nucleatum*has been shown to be associated with liver involvement[26], explaining patient's scleral icterus bilaterally, which may have caused her vision to be temporarily bright and blurry in the ER[18].

Our patient's outside hospital admission included blood cultures, which successfully identified *Fusobacterium nucleatum* as the source of her infection. This pathogen may take up to 5-8 days to culture stressing the importance to administer empiric antibiotics with anaerobic coverage and varied diagnostic studies. Additionally, early detection of the pathogen is imperative to foster favorable prognosis. The rapid administration of treatment depends on the clinician's awareness of LS and considering it as a differential diagnosis. It is not unreasonable to suspect LS in any young adult who presents with ongoing fevers in the recent episode of pharyngitis, even when source is unknown or presumed like *streptococcus pyogenes* .

Literature shows other patients with Lemierre's syndrome have presented with severe sepsis and abdominal pain, treated with ampicillin-sulfabactum and metronidazole intravenously for three weeks, followed by a three-week course of oral amoxicillin/clavulanate, intravenous hydration, inotropic support, and thoracostomy tube drainage of pleural effusion[12]. Lack of characteristic neck symptoms or a negative initial neck ultrasound exam does not rule out LS.[6] Case studies have demonstrated metastatic infections in the lung and brain including meningitis requiring aggressive management and therapies[5, 19, 26]. Another case study demonstrated patient with LS showing septic arthritis of right shoulder, as well as parapharyngeal abscess extending from base of skull to thoracic inlet, complicated by right IJV and subclavian vein thrombosis, and multiple lung emboli. Patient improved with oral clindamycin and metronidazole, IV gentamicin, IV piperacillin and tazobactam, incision and drainage of parapharyngeal abscess, and drain left in-situ[13].

There are few case reports out of Belgium that report*Fusobacterium* as a possible complication of COVID-19 virus, as none of the patients had any risk factors for *F. nucleatum*bacteremia. All patients were adults with other comorbid factors[21]. They were tested COVID PCR positive for SARS-CoV-2, which resulted in digestive tract invasion and hence leading to *Fusobacterium* bacteremia[21]. Other organisms besides *Fusobacterium necrophorum* can cause LS such as*Streptococcus* , *Proteus* , *Bacteroides* , and *Peptostreptococcus* . In this particular case report, patient had severe respiratory and renal involvement without thrombosis of the jugular vein similar to our case[22].

Lastly, it is imperative to not delay seeking medical attention due to concerns about the SARS-CoV-2 outbreak, as one patient with delayed care presented with atypical Lemierre's syndrome involving the brain, liver, and lungs following a dental infection, ultimately resulting in serious and complex sequelae[26].

4. Conclusion

Our case report highlights the fact that although LS is a rare medical condition, it can be deadly. It is essential to recognize early clinical presentation, especially in young adults presenting with sore throat and fever or cough. Early recognition of LS will ensure favorable prognosis. In our patient's case, although lungs are the most common areas of septic emboli, her osteomyelitis is suspicious to be secondary to septic emboli, suggesting that other organs are not immune to disease pathogenesis but she did not have internal jugular vein thrombosis, which is required to make the diagnosis.

We hope to raise awareness to clinicians, especially in the era of SARS-CoV-2, including family medicine practitioners and pediatricians to maintain high level of clinical suspicion for any adolescent or young adult patient who presents with unexplained, persistent fever after oropharyngeal infection to facilitate diagnostic studies to implement appropriate therapies and prolong survival and favorable outcomes to prevent the most dire consequences.

Conflicts of Interest

The authors declare that they have no conflicts of interest. Family gave permission to publish this case report.

References

1. Cheung, W., et al. Fusobacterium Elusive cause of life-threatening septic thromboembolism. Can Fam Physician. 2007 Sep; 53(9): 1451–1453.

2. Hagelskjaer LH, Prag J, Malczynski J, Kristensen JH. 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.

3. 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.

4. Weesner CL, Cisek JE. Lemierre's syndrome: the forgotten disease. Ann Emerg Med. 1993;22(2):256–8

5. Dool H, Soetekouw R, van Zanten M, Grooters E. Lemierre's syndrome: three cases and a review. Eur Arch Otorhinolaryngol. 2005;262(8):651–4. Epub 2004 Dec 15.

6. Nguyen-Dinh KV, Marsot-Dupuch K, Portier F, Lamblin B, Lasjaunias P. Lemierre syndrome: usefulness of CT in detection of extensive occult thrombophlebitis. J Neuroradiol. 2002;29(2):132–5.

7. Hagelskjaer LH, Kristensen L, Prag J. Human necrobacillosis, with emphasis on Lemierre syndrome. Clin Infect Dis. 2000;31(2):524–32.

8. Williams A, Nagy M, Wingate J, Bailey L, Wax M. Lemierre's syndrome: a complication of acute pharyngitis. Int J Pediatr Otorhinlaryngol. 1998;45(1):51–7.

9. Kuppalli K, Livorsi D, Talati NJ, Osborn M. Lemierre's syndrome due to Fusobacterium necrophorum. Lancet Infect Dis 2012; 12:808.

10. Jensen A, Hagelskjaer Kristensen L, Prag J. Detection of Fusobacterium necrophorum subsp. funduliforme in tonsillitis in young adults by real-time PCR. Clin Microbiol Infect 2007; 13:695.

11. L. Hagelskjaer Kristensen, J. Prag Lemierre's syndrome and other disseminated Fusobacterium necrophorum infections in Denmark: a prospective epidemiological and clinical survey Eur J Clin Microbiol Infect Dis, 27 (2008), pp. 779-789

12. Hoehn S, Dominguez TE.Lemierre's syndrome: an unusual cause of sepsis and abdominal pain. Critical Care Medicine, 01 Jul 2002, 30(7):1644-1647

13. Chan JKC, Rashid M, Karagama YG, Bhalla RK. An Unusual Presentation of Lemierre's Syndrome: Case Report and Review of the Literature. Am J Otolaryngol Head Neck Surg. 2020; 3(3): 1093.

14. Riordan T, Wilson M. Lemierre's syndrome: more than a historical curiosa. Postgrad Med J. 2004;80(944):328.

15. Han, Yiping W. Fusobacterium nucleatum: a commensal-turned pathogen. Curr Opin Microbiol. 2015 Feb; 0: 141–147.

16. Brady W. Allen; Fatima Anjum; Thomas P. Bentley. Lemierre Syndrome. Treasure Island (FL): StatPearls Publishing; Jan 2021

17. Camelo C , Brandao M , Fernandes L , et al . Lemierre syndrome: a case report. J Vasc Bras 2015;14:253–7.Google

18. Moore BA , Dekle C , Werkhaven J . Bilateral Lemierre's syndrome: a case report and literature review. Ear Nose Throat J 2002;81:234–52.

19. Sudarshana Murthy KA , Thippeswamy T , Kiran HS , et al . Case report: the 'forgotten disease' (or the never known). JAPI 2013;61:754–7.Google

20. Johannesen KM , Bodtger U . Lemierre's syndrome: current perspectives on diagnosis and management. Infect Drug Resist 2016;9:221–7.

21. Wolff L, Martiny D, Deyi V, Mailart E, Clevenbergh P, Dauby N. COVDID 19 associated Fusobacterium nucleatum Bacterimia, Belgium. Emerging Infectious Diseases. Vol 27, No 3, March 2021

22. Rana M, Kumar Y, Lashari A and Mady A. Human infection with Fusobacterium necrophorum without Jugular Venous Thrombosis: A Varied Presentation of Lemierre's Syndrome. Case Reports in Infectious Diseases. March 2020

23. Repper DC, Arrieta AC, Cook JE, Renella P. A care of Lemierre Syndrome in the Era of COVID-19: All that Glitters is not Gold. Pediatric Infectious Disease J. 2020 Dec ; 39 (12):e445-447. Doi: 10.1097

24. Jassem E, Kedzia A, W-Goszka L, Mincewicz H, Krzywiceki A andSlominski JM. Non spore forming anaerobic bacteria in bronchoalveolar lavage fluid of patients with pneumonia during the course of lung cancer. Pneumonol Alergol Pol. 1997;65(9-10):643-8.

25. Bingula, R., Filaire, E., Molnar, I. et al. Characterisation of microbiota in saliva, bronchoalveolar lavage fluid, non-malignant, peritumoural and tumour tissue in non-small cell lung cancer patients: a cross-sectional clinical trial. Respir Res 21, 129 (2020). https://doi.org/10.1186/s12931-020-01392-2

26. Howley F, O'Doherty L, McEniff N, et alLate presentation of 'Lemierre's syndrome': how a delay in seeking healthcare and reduced access to routine services resulted in widely disseminated Fusobacterium necrophorum infection during the global COVID-19 pandemicBMJ Case Reports CP 2020;13:e239269.

27. Pastorino A, Tavarez MM. Incision and Drainage. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2021 Jan-.

28. Lemierre A. On certain septicemias due to anaerobic organisms. Lancet. 1936;1:701–3.

29. Lemierre's syndrome: new insights into an old disease. Stallworth JR, Carroll JM Clin Pediatr (Phila). 1997 Dec; 36(12):715-7.