CASE REPORT

Lemierre Syndrome Three Weeks After COVID-19 Infection

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INTRODUCTION

Lemierre's syndrome is a rare disease that classically presents with septicemia, thrombophlebitis, and distal embolization that develops 1-3 weeks after an oropharyngeal infection. *Fusobacterium necrophorum* is the causative pathogen in the majority of cases. It has been hypothesized that preceding oropharyngeal infection leads to mucosal damage, which allows the penetration of Fusobacterium into the pharyngeal space and internal jugular vein. There have been reported links between Lemierre's syndrome and viral infections such as Epstein Barr virus and influenza [1-3]. Early diagnosis of Lemierre's syndrome can be challenging due to its overlapping symptoms with other infections. Moreover, Fusobacterium grows slowly in cultures resulting in further delay in diagnosis. The timely administration of appropriate antibiotic therapy is crucial as mortality without antibiotic administration can reach up to 90% [4]. We present the case of a 29-year-old male who was diagnosed with Lemierre's syndrome 3 weeks after a COVID-19 infection. He presented with sepsis syndrome, solitary lung abscess, and cutaneous infarcts. The diagnosis was established after blood cultures grew *Fusobacterium necrophorum* and imaging revealed left internal jugular thrombus. This case demonstrates some of the difficulties in early diagnosis of Lemierre's syndrome in the setting of the COVID-19 pandemic due to similarities in presentation.

CASE PRESENTATION

A 29-year-old healthy male presented to the emergency department with a 2-day history of fever, chills, nausea, and intractable vomiting. He denied any diarrhea, cough, dyspnea, headache, neck stiffness, joint pain, rash, or dysuria.

Three weeks prior, he was diagnosed with a mild COVID-19 infection. Symptoms at the time consisted of sore throat, sinus pressure, malaise, and submandibular fullness suggestive of lymphadenopathy. The symptoms lasted for a few days and resolved spontaneously without therapeutics.

The patient has no medical or surgical history and takes no medications. There is no significant family history. Nine months prior

to presentation, he was vaccinated with two doses of the Pfizer-BioNTech COVID-19 vaccine. He reports heavy inhaled marijuana use but denies any other illicit drug abuse. He does not smoke or drink. There has been no recent travel.

On exam, the patient was febrile with temperature of 102.9F, tachycardic (heart rate in the 120's), and mildly hypertensive with blood pressures in the 150's/80's. Oropharyngeal exam showed dry mucous membranes without evidence of oropharyngeal erythema or exudates. There was generalized discomfort on abdominal exam without hepatosplenomegaly. There were no murmurs, rubs, or gallops on cardiac auscultation. Lungs were clear to auscultation, and there was no tachypnea, accessory muscle use, crackles, or rhonchi.

Laboratory findings on admission (table 1) were significant for a white blood cell count of 16.0 K/μL with 93% neutrophils and no bands. Hemoglobin was 12.8 g/dL, and platelets were normal at 192,000 K/μL. Chemistries showed creatinine of 1.2 mg/dL and mild metabolic acidosis with a bicarbonate level of 21 mmol/L and anion gap of 16. Procalcitonin was elevated at 12.20 μg/mL, ESR was 72 mm/hr, and C-reactive protein was over 300.0 mg/L. SARS-CoV-2 RT-PCR was positive with an ORF target count of 37.8 consistent with viral remnants from recent infection. Blood cultures were sent. Urine studies (table 2) showed 1-2 WBC's, which was not consistent with infection. There was, however, 4-5 RBC's and 1+ protein.

He was presumed to have gastroenteritis and was admitted for intravenous hydration and symptomatic treatment. On the 2nd day of hospitalization, he developed new onset severe pain and erythema of the distal phalanges of the 2nd to 5th digits of the right hand that eventually progressed to partial skin necrosis (figure 1). Radial and ulnar arterial pulses were strong. This raised the suspicion for septic emboli.

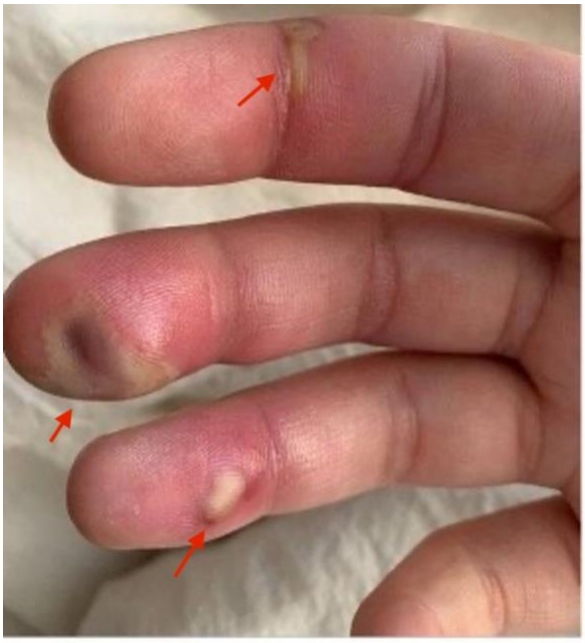
TABLE 1: Laboratory values

Test	Value
WBC	16.0 K/μL
Neutrophils	93.3%
Bands	0%
Hemoglobin	12.8 g/dL
Hematocrit	41.0%
Platelets	192 K/μL
Blood Urea Nitrogen	13 mg/dL
Creatinine	1.2 mg/dL
Bicarbonate	21 mmol/L
Anion gap	16 mmol/L
Lipase	16 U/L
Aspartate aminotransferase	34 U/L
Alanine aminotransferase	77 U/L
Alkaline phosphatase	117 U/L
C-reactive protein	>300.0 mg/L
Erythrocyte sedimentation rate	72 mm/hr

TABLE 2: Urine studies

Test	Value
WBC	1-2/HPF
RBC	6-10/HPF
Bacteria	None seen
Squamous epithelial	None seen
Protein	52.0 mg/dL
Creatinine	177.2 mg/dL
Urine protein: creatinine ratio	0.293

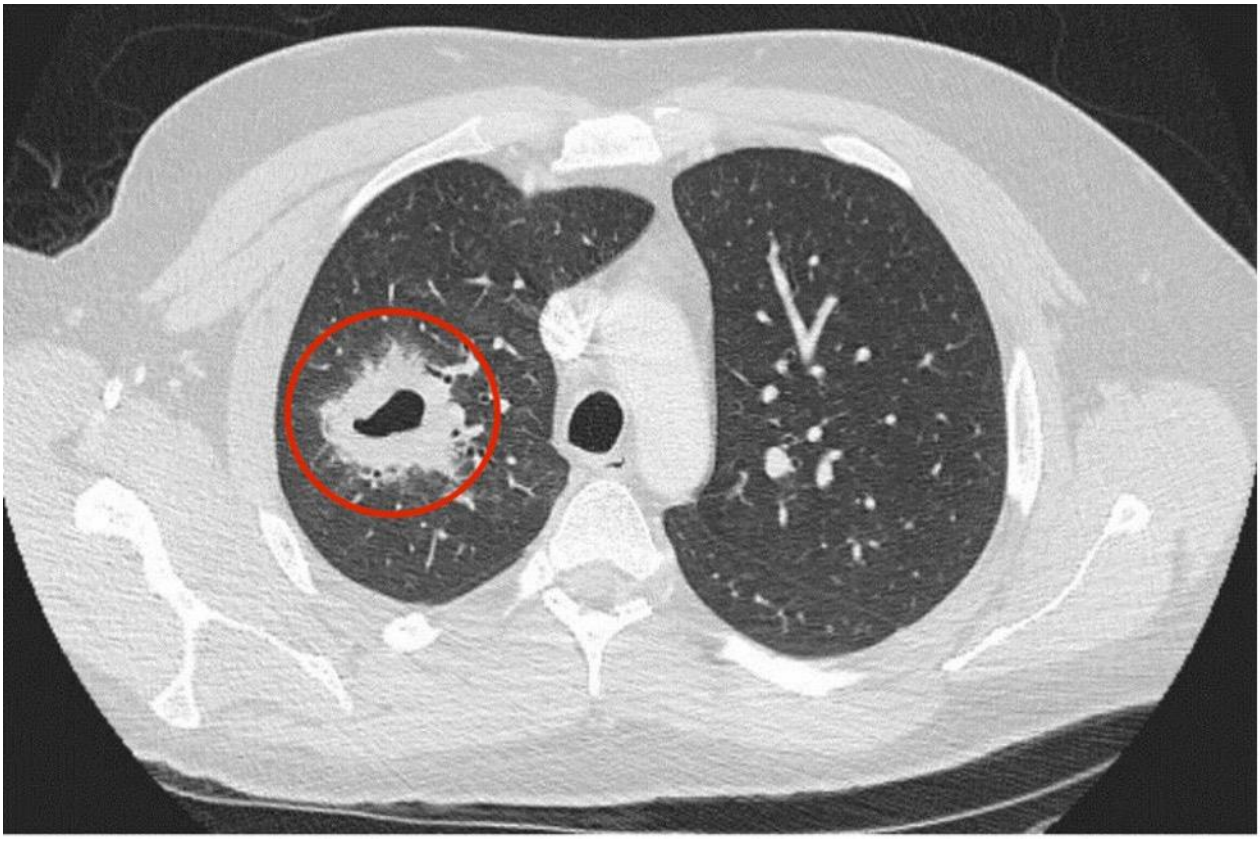
FIGURE 1:
Septic emboli with partial skin necrosis



Right hand distal phalanges septic emboli with partial skin necrosis (red arrows).

An investigation for potential source of septic emboli was pursued. Doppler ultrasound did not reveal septic thrombi in the right upper extremity arteries. Transthoracic echocardiogram and subsequently transesophageal echocardiogram did not show evidence of vegetations. CT chest with contrast showed a thick walled 3.7 cm right upper lobe cavitary lesion with air fluid levels (figure 2). On the 3rd day of hospitalization, blood cultures grew gram-negative coccobacilli in the anaerobic bottles after two days of growth. An infectious disease specialist was consulted. IV ampicillin/sulbactam and vancomycin were started. It was postulated that intractable nausea and vomiting prior to admission might have led to aspiration. On the 5th day of hospitalization, the pathogen in the blood cultures was identified as *Fusobacterium necrophorum* after four days of growth. This raised the concern for Lemierre's syndrome. Vancomycin was discontinued and

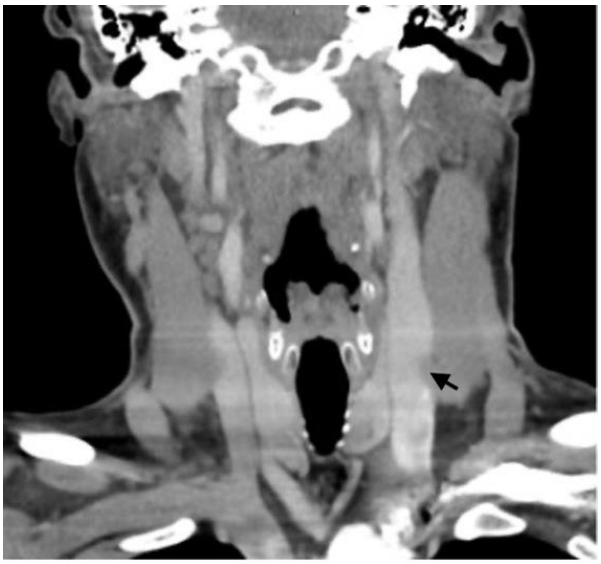
FIGURE 2: Pulmonary abscess



CT chest showing thick walled 3.7 cm abscess in the right upper lobe (outlined by red circle)

ampicillin/sulbactam was switched to ertapenem for broader coverage as antibiotic sensitivity was not performed. Follow-up blood cultures were negative. CT soft tissue of the neck was obtained and revealed an ill-defined focus of low attenuation in the left internal jugular vein (figure 3). Vascular ultrasound confirmed the presence of non-occlusive thrombus in the proximal left internal jugular vein (figure 4). This established the diagnosis of Lemierre's syndrome.

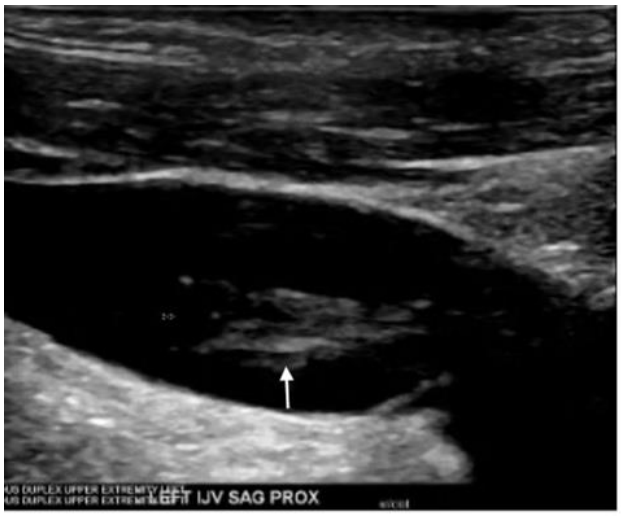
FIGURE 3: Left internal jugular thrombus



CT neck showing low attenuation in the left internal jugular vein consistent with thrombus (black arrow)

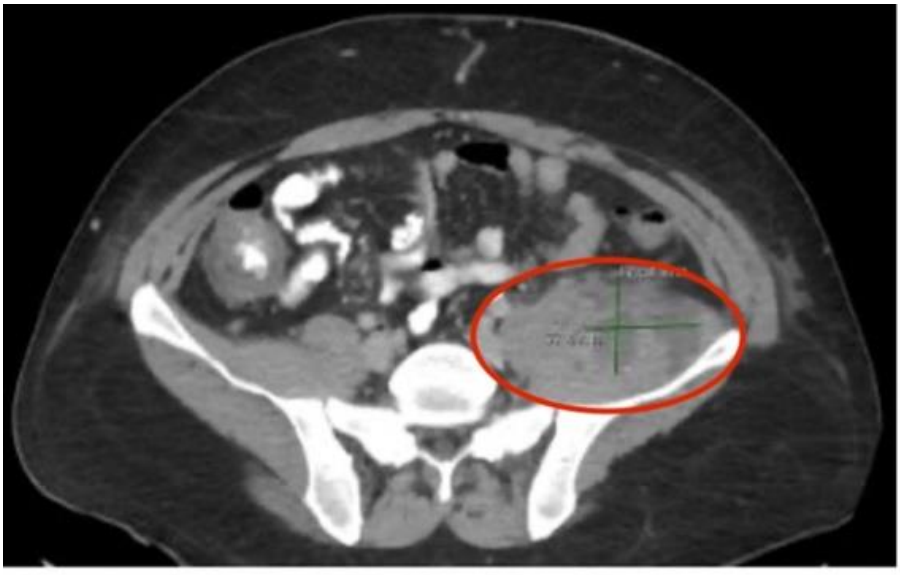
On the 6th day of hospitalization, the patient developed increasing left hip pain with difficulty bearing weight. CT abdomen/pelvis showed a new multiloculated fluid collection in the left iliopsoas measuring 5.7 x 4.8 cm (figure 5). CT-guided needle aspiration yielded 30 ml of purulent fluid. Gram stain of fluid showed many polymorphonuclear leukocytes and rare gram-positive cocci. Culture was negative.

FIGURE 4: Ultrasound showing left internal jugular thrombus



Sagittal image of the left internal jugular vein ultrasound showing post occlusive thrombus (white arrow)

FIGURE 5: Left iliopsoas muscle abscess



CT abdomen/pelvis with contrast showing left iliopsoas abscess (low attenuation regions in the red circle)

The patient defervesced, and white blood cell count normalized to 11.1 K/μL on the 10th day of hospitalization. He was discharged on ertapenem for 6 weeks.

With regards to the mild proteinuria and microscopic hematuria, nephrology was consulted, and a comprehensive workup was pursued to exclude glomerulonephritis. Antinuclear antibodies, antineutrophilic cytoplasmic antibodies, anti-glomerular basement membrane antibodies, and antistreptolysin O antibodies were negative. Complement C3 was normal at 161.0, and complement C4 was normal at 22.0. HIV test was negative. Hepatitis B surface antibody, hepatitis B surface antigen, hepatitis B core antibody, and hepatitis C antibody were negative. Random urine protein electrophoresis and serum electrophoresis did not show monoclonal proteins. An etiology for the microscopic hematuria and proteinuria was not determined, but it was speculated that it might be related to microscopic septic emboli that were not visible on CT abdomen/pelvis. Other possible etiologies that were considered included post-infectious glomerulonephritis or COVID-related renal injury.

DISCUSSION

Lemierre's syndrome is an uncommon disease with an estimated incidence of 1/1,000,000 [2]. It usually affects adolescents and young adults with a 2:1 male predominance [5]. The most frequent culprit pathogen is *F. necrophorum*. Cases of Lemierre's syndrome declined with the widespread use of antibiotics to treat oropharyngeal infections, leading it to be dubbed "the forgotten disease" [6]. With the decreased use of empiric antibiotics in the antibiotic stewardship era, there has been an increase in reported cases. The classic presentation of Lemierre syndrome is septicemia, thrombophlebitis, and distal embolization that usually develops 1-3 weeks after an oropharyngeal infection. The mechanism is thought to be from local invasion into the pharyngeal space and internal jugular vein, leading to septic thrombophlebitis and septic embolism.

There have been reports of certain infections preceding the onset of Lemierre's syndrome. Epstein-Barr virus is the main pathogen. Other pathogens, such as cytomegalovirus, influenza, and *Mycoplasma pnemoniae*, have also been reported [1,7]. It is speculated that pathogens such as Epstein-Barr virus may increase susceptibility to Lemierre's syndrome by multiple mechanisms, including altered mucosa, lymphatic obstruction, deficient translocation of leukocytes, and impaired immunoglobulin production due to T-cell suppression of B cells [8]. In our patient, Lemierre's syndrome occurred 2 weeks after contracting COVID-19. As the SARS-CoV-2 virus affects the oropharyngeal mucosa, it is possible that it may have predisposed the patient to Lemierre's syndrome by a similar mechanism, although specific causation studies will need to be done to accurately determine this.

Since COVID-19 was declared a global pandemic in March 2020, millions have been affected worldwide, and there has been increased burden on health care systems throughout the world. The diagnosis of Lemierre's syndrome can be challenging if it occurs during a COVID-19 infection. Both entities can begin with sore throat and fever and can lead to sepsis syndrome and thrombosis. The majority of thrombotic episodes in COVID-19 are venous, however arterial thrombosis such as stroke and rarely limb ischemia can occur [9,10]. While moderate to severe forms of COVID-19 typically present with respiratory symptoms, Lemierre's syndrome tends to have more diverse symptoms depending on the location of the septic emboli. Unilateral neck swelling and tenderness is present in 25% to 45% of cases and is an early sign of internal jugular

thrombosis [11]. The most common site of septic emboli are the lungs, where manifestations include necrotic pulmonary emboli and empyema. Other common sites include joints, meninges, liver, kidney, and bones [12]. Septic shock and ARDS requiring mechanical ventilation can occur in up to 10% of patients.

Multisystem inflammatory syndrome in adults (MIS-A) is a rare post-infectious complication of COVID-19 and is an important differential diagnosis to consider in this setting as it can occur 2-5 weeks after a COVID-19 infection and, like Lemierre's syndrome, occurs predominantly in younger age groups [13]. MIS-A is a clinical entity that involves hyperinflammation, shock, and heterogenous extrapulmonary manifestations including cardiac (myocarditis, pericarditis, coronary artery dilation), gastrointestinal (vomiting, diarrhea, abdominal pain), dermatologic (rash, mucocutaneous lesions), AKI, and thrombosis.

In our patient, bacteremia was suspected after he developed septic emboli of the right-hand digits and a solitary pulmonary abscess was found on imaging. Lemierre's syndrome was confirmed after thrombosis was seen in the internal jugular vein and blood cultures grew *F. necrophorum*

Antimicrobial agents are the mainstay treatment for Lemierre's syndrome. Fusobacterium necrophorum has been shown to be resistant to several antibiotics and to have beta-lactamase activity in up to a quarter of isolates [15]. Ertapenem was used in our patient both for its stability against beta-lactamase and for the relative ease of dosing compared to ampicillin/sulbactam that was initially started. The duration of the antibiotic use is not well established, but typically a prolonged course up to 6 weeks is administered [6]. Anticoagulation is sometimes used in Lemierre's syndrome, however, a meta-analysis in 2020 of 194 patients showed no statistically significant reduction in mortality with use of anticoagulation in Lemierre syndrome patients [16]. No specific recommendations are available regarding the treatment of COVID-19 in the setting of secondary bacterial infections, however COVID-19 treatments have been associated with an increased risk of bacterial infection, therefore they should be used with caution [17].

CONCLUSION

Symptoms of COVID-19 predominantly involve the respiratory system, however extrapulmonary manifestations are frequently encountered. These include sepsis syndrome, sore throat, and thromboses that can have similar appearance to Lemierre's syndrome. Therefore, the diagnosis of Lemierre's syndrome can be challenging if it occurs during a COVID-19 infection. Fusobacterium, the most common causative pathogen, is an anaerobic bacterium that requires 6-8 days to grow in cultures and thus adds to the difficulty in reaching the accurate diagnosis. Maintaining a high level of clinical suspicion is essential to early detection of Lemierre's syndrome.

Notes

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