A Case of Lemierre's Syndrome in Association with Liver Abscess without Any Other Metastatic Lesions

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Abstract

Lemierre's syndrome (LS) is characterized by pharyngitis followed by septicemia, internal jugular vein thrombophlebitis, and metastatic embolization in general. LS is commonly caused by *Fusobacterium necrophorum*. Herein, we present a case of LS with liver abscesses that presented as a sole metastatic lesion. We were not able to diagnose LS until *Fusobacterium necrophorum* was isolated due to the lack of the common involvement. Doripenem was effective against the pathologic features including the liver abscesses. LS should be taken into consideration when clinicians find liver abscesses following pharyngitis even when the common complications of LS are not detected.

Key words: Lemierre's syndrome, liver abscess, *Fusobacterium necrophorum*, carbapenem, pharyngitis

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Introduction

Lemierre's syndrome (LS) was first described by Courmont and Cade in 1900 (1) and it was well characterized by Lemierre in 1936 (2). LS is characterized by pharyngitis followed by septicemia, internal jugular vein (IJV) thrombophlebitis, and metastatic embolization to various organs, especially to the lungs (3, 4). The most common causative pathogen is *Fusobacterium necrophorum*. LS generally occurs in previously healthy young adults. In the pre-antibiotic era, LS was common and often fatal (2). However, there has been a substantial decrease in both the morbidity and mortality of LS along with the development and the widespread use of antibiotics for the treatment of pharyngeal infections. Nonetheless, recent reports have described the increasing incidence of LS (5-7). The cause of the increase is uncertain, but the increasingly judicious use of antimicrobial agents to treat pharyngeal infections and a change in the antibiotic susceptibility pattern of *Fusobacterium necrophorum* might be related to this increase (5). Although the mortality rate for LS has improved since the pre-antibiotic era, it is currently reported to be approximately 10% (3, 4, 8). Accordingly, early diagnosis and appropriate treatment are essential

to improve the mortality rate. However, the diagnosis of LS is often not made until the isolation of *Fusobacterium necrophorum* from blood culture (4). Furthermore, when common complications such as IJV thrombophlebitis or pulmonary involvement are not overt, it becomes more difficult to diagnose LS in an expedient fashion.

Here, we describe a case of LS with liver abscesses that presented as a sole metastatic lesion, which is quite rare in LS (3). We were not able to diagnose LS based on clinical findings soon after the patient was admitted due to the lack of IJV thrombophlebitis and pulmonary involvement. Complementary examinations detected liver abscesses and sepsis induced by *Fusobacterium necrophorum*, which led to the diagnosis of LS. Doripenem (DRPM) was effective in treating this case, including the liver lesions.

Case Report

A previously healthy 44-year-old man visited a local clinic complaining of high fever and a sore throat. He was initially diagnosed with pharyngitis and was treated with a one-week course of oral cefdinir (CFDN). Thereafter, the sore throat improved, but a low-grade fever continued. Ten days after the onset of a sore throat, the patient developed a

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Table 1. Laboratory Data on Admission

WBC	15,190	/μL	PT	12.8	sec
RBC	473×10 ⁴	/μL	PT-INR	1.23	
Hemoglobin	16.0	g/dL	APTT	39.3	sec
Hematocrit	46.5	%	FDP	<10	μg/mL
Platelet	61,000	/μL	Immunoglobulin G	1,548	mg/dL
Total protein	6.1	g/dL	Immunoglobulin A	215	mg/dL
Albumin	3.5	g/dL	Immunoglobulin M	196	mg/dL
BUN	23	mg/dL			
Creatinine	1.2	mg/dL	<i>Entamoeba histolytica</i> antibody		
Total Bilirubin	2.4	mg/dL	negative		
AST	76	IU/L	Dipstick urine examination		
ALT	160	IU/L	2+ proteinuria		
LDH	265	mg/dL	2+ hematuria		
ALP	679	IU/L	On urine microscopy		
γ-GTP	697	IU/L	RBC 1-4 / HPF		
CRP	25.0	mg/dL	WBC <1/ HPF		

WBC: white blood cell count, RBC: red blood cell count, BUN: blood urea nitrogen, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, ALP: alkaline phosphatase, γ-GTP: γ-glutamyltranspeptidase, CRP: C-reactive protein, PT: prothrombin time, INR: international normalized ratio, APTT: activated partial thromboplastin time, FDP: fibrin and fibrinogen degradation products, HPF: high-power field

Figure 1. Schematic diagram of the patient's clinical course. High-grade fever appeared after admission but was alleviated by treatment with Doripenem (DRPM). A coagulation disturbance including thrombocytopenia was successfully treated.

high fever. Thirteen days after the onset of this sore throat, he visited another clinic and was referred to our hospital for further examination and treatment.

At the time of admission, the patient was 173 cm tall and weighed 82 kg. He looked unwell and had a blood pressure of 98/59 mmHg, a pulse rate of 120/min, a temperature of 38.9°C and a percutaneous oxygen saturation of 97%. He was clearly conscious and was not icteric. The patient did not have a sore throat, neck tenderness or respiratory symptoms. The oropharynx appeared normal. Abdominal examination revealed mild right hypochondrial pain. Examinations of the respiratory and cardiovascular systems revealed no abnormality. Laboratory data on admission (Table 1) revealed a strong inflammatory reaction involving 25.0 mg/dL of C-reactive protein (CRP), thrombocytopenia, the elevation

of liver enzymes and mild renal dysfunction. The clinical course is shown in Fig. 1. At first, the focus of the infection could not be identified. Then, a viral infection was suspected for the fever due to the mild liver injury and thrombocytopenia observed. However, certain bacterial infections, such as a urinary tract infection, were also simultaneously suspected because the white blood cell count (WBC) and the CRP level were increased. The patient was therefore intravenously treated with cefotiam (CTM) after a blood culture was obtained. After the patient was admitted, the degree of right hypochondrial pain improved, but the fever spike continued with rigor despite the administration of CTM. On the third hospital day, laboratory tests revealed sustained high-grade inflammation (WBC 21,180/μL, CRP 20.9 mg/dL), marked thrombocytopenia (platelets 23,000/μL) and im-

Figure 2. Imaging examinations. (A) Computed tomography (CT) revealed multiple small, low-density lesions in the liver. (B, C) In the magnetic resonance images, these lesions exhibited hypointensity on T1-weighted images (B) and hyperintensity on T2-weighted images (C). (D) On the seventeenth hospital day, liver abscesses were no longer detectable by CT.

pairment of coagulation status (fibrin and fibrinogen degradation products: 10-19 $\mu\text{g/mL}$, anti-thrombin III 59%). Subsequent abdominal computed tomography (CT) revealed multiple small, low-density lesions in the liver (Fig. 2A), which were visualized as small, low-echoic lesions on abdominal ultrasonography. Magnetic resonance imaging (MRI) showed that these lesions exhibited hypointensity on T1-weighted images (Fig. 2B) and hyperintensity on T2-weighted images (Fig. 2C). These findings were compatible with the existence of multiple liver abscesses. *Entamoeba histolytica* antibody staining was negative. The liver abscesses were considered to have caused the fever. In addition, disseminated intravascular coagulation (DIC) was indicated based on scoring criteria established by the Japanese Association for Acute Medicine for DIC. Taking these clinical findings into consideration, the antibiotic was changed to DRPM, and intravenous immunoglobulin therapy was initiated. Gabexate mesylate, a transfusion of platelets and human anti-thrombin III were also administered for the treatment of DIC. These treatments were effective and gradually ameliorated the patient's condition. On the tenth day of the patient's hospital stay, *Fusobacterium necrophorum* was isolated from the blood culture drawn on the second hospital day. At last, the patient was diagnosed LS according to the definition reported by Riordan (3), although Doppler ultrasonography did not detect IJV thrombophlebitis. The isolated *Fusobacterium necrophorum* was sensitive to ampicillin, piperacillin, cefazolin, sulbactam/cefoperazone, cefotaxime, ceftazidime, imipenem (IPM), meropenem (MEPM), DRPM, clindamycin (CLDM), clarithromycin, and levofloxacin (LVFX), and resistant to teicoplanin and vancomycin. Based on this microbial analysis, we continued treatment

with DRPM. On the seventeenth hospital day, CT showed that the liver abscesses had disappeared (Fig. 2D). On the nineteenth hospital day, the patient was switched from treatment with antibiotics to treatment with oral LVFX. The strain of *Fusobacterium necrophorum* that had infected this patient was indeed sensitive to oral LVFX. The patient was discharged and no infectious symptoms have been observed since discharge.

Discussion

The definition of LS has not yet been established. Riordan reviewed numerous published cases of LS and established the following definition (3): (i) history of angina in the preceding 4 weeks or compatible clinical findings, (ii) evidence of metastatic lesions, (iii) evidence of IJV thrombophlebitis or isolation of *Fusobacterium necrophorum* or *Fusobacterium* spp. from blood cultures or a normal sterile site. Early diagnosis and prompt treatment with appropriate antibiotics are important to reduce the likelihood of mortality (4, 9). Chirinos et al. reported that in 69.7% of LS cases, the first clue to the diagnosis was the finding of *Fusobacterium necrophorum* in culture results rather than clinical signs or symptoms (4), which indicates that many clinicians will not be able to diagnose LS based on early clinical features. *Fusobacterium necrophorum* usually takes 2 to 7 days to grow in culture (10); therefore, fatal outcomes may result if proper treatment is not administered until the isolation of *Fusobacterium necrophorum*. In the present case, a diagnosis of LS could not be made during the early post-admission period. Reports based on the results of blood culture confirmed this diagnosis on the tenth hospital day. In particular, the lack of common complications, such as IJV thrombophlebitis or pulmonary involvement, resulted in a delayed diagnosis. LS should be taken into consideration when a previously healthy adult presents with acute sepsis following pharyngeal infection, despite the lack of any common complications associated with LS.

Septic embolizations of LS occur in various organs. Typically, IJV thrombophlebitis can give rise to septic emboli. However, IJV thrombophlebitis is only documented in 59-72% of patients with LS (3, 4). In such cases, septic emboli may spread via microvessels near the pharynx that are upstream of IJV, such as the tonsillar vein and the peritonsillar vein. On the other hand, liver abscess, which was the only metastatic complication in this case, is rare and identified in only 2-4% of LS cases (3, 4). A PubMed search revealed 13 reports of LS with liver abscess (Table 2). Liver abscesses are often multiple rather than solitary. Liver dysfunction was detected frequently (in 10 of these 13 cases). However, abnormal liver function is not a characteristic finding of liver abscess in the context of LS because it is found in 30-50% of LS cases regardless of the existence of a liver abscess (3, 4). Among these 13 cases, there were only 5 in which the liver abscess was the only metastatic lesion, which implies that liver abscess as the sole systemic mani-

Table 2. Clinical Features of Reported Cases of Lemierre's Syndrome with Liver Abscess

Number (ref)	Age /sex	Antibiotics for pharyngitis	Liver dysfunction	Morphology of liver abscess	IJV thrombophlebitis	Other metastatic lesions	Antibiotics given
1. (16)	11 y/NR	NR	Yes	NR	NR	NR	CLDM+MTZ+LMOX
2. (17)	17 y/NR	NR	Yes	multiple	No	empyema	CXM+GM+MTZ
3. (11)	17 y/F	No	Yes	multiple	Yes	lung	NFPC+CTRX+MTZ
4. (18)	18 y/M	No	Yes	single	Yes	lung, empyema	CFPM+MTZ
5. (19)	18 y/M	PC	Yes	multiple	No	lung	CXM+MTZ
6. (20)	19 y/F	AMPC	Yes	multiple	No	empyema	PC+MTZ+CPFX
7. (21)	32 y/M	No	NR	single	Yes	lung, empyema	CLDM+MEPM+TEIC
8. (15)	70 y/F	CAM	Yes	single	Yes	lung, thyroid	IPM+MTZ
9. (22)	8 m/M	PC	No	multiple	No	No	ABPC+GM+MTZ
10. (23)	5 y/F	PC	Yes	single	No	No	PC+CP
11. (24)	21 y/M	AMPC	No	multiple	No	No	TAZ+MTZ
12. (25)	22 y/M	No	Yes	multiple	No	No	GM+MTZ+CTRX+CLM
13. (this case)	44 y/M	CFDN	Yes	multiple	No	No	DRPM

PC: penicillin, AMPC: amoxicillin, CAM: clarithromycin, CFDN: cefdinir, MTZ: metronidazole, LMOX: moxalactam, CXM: cefuroxime, GM: gentamicin, NFPC: nafcillin, CTRX: ceftriaxone, CFPM: cefepime, CPFX: ciprofloxacin, CLDM: clindamycin, MEPM: meropenem, TEIC: teicoplanin, IPM: imipenem, ABPC: ampicillin, CP: chloramphenicol, TAZ: tazobactam, DRPM: doripenem, NR: non-referred, Ref: reference, IJV: internal jugular vein

festation in LS patients is quite rare. It is not clear why septic emboli were found only in the liver. Chirinos et al. found that early antibiotic treatment could prevent the metastatic spread of infection through embolization (4). In 4 of these 5 cases, antibiotics were administered to treat pharyngitis; therefore, it is possible to assume that the prescription of antibiotics for pharyngitis prevented the development of septic emboli in all organs other than the liver. It is unclear why this approach to treatment was not able to prevent the development of a liver abscess. Nonetheless, administering antibiotic treatment to all patients with pharyngitis to prevent the spread of septic emboli in case of LS is not recommended because LS is still rare and the abuse of antibiotics induces resistance. Therefore, when clinicians examine a previously healthy patient with a liver abscess after pharyngitis, even if liver pathology represents the only extrapharyngeal lesion, it is necessary to consider the possibility of LS and treat the patient with the appropriate antibiotics in an expedient fashion. Regarding therapeutic interventions, drainage of the liver abscess was performed in 8 of these 13 cases. According to Stallworth and Carroll, drainage of any LS abscesses is generally necessary for successful treatment (11). In the present case, all liver abscesses were small, and there were no drainable lesions.

Fusobacterium necrophorum is usually susceptible to penicillin, CLDM, metronidazole (MTZ), and chloramphenicol. However, the resistance rates of *Fusobacterium necrophorum* to penicillin and macrolides were reported to be as high as 22% and 66%, respectively (7, 12, 13). The strain of *Fusobacterium necrophorum* isolated in the case described

here was sensitive to the drugs administered. Furthermore, in LS, mixed infections involving organisms such as oral streptococci may occur (10). Therefore, combination therapy with penicillin and MTZ is generally recommended (3). Recently, there have been several reports that combination therapy with carbapenems and MTZ or CLDM is effective in the treatment of LS (14, 15). However, the efficiency of monotherapy with carbapenems for LS has not been reported. In the present case, we initially treated with CTM, but CTM was not effective. Then, DRPM was substituted for CTM, which led to an improvement in the patient's overall clinical features. In this case, when *Fusobacterium necrophorum*, which was sensitive to DRPM, had been isolated on the tenth hospital day, the patient had already improved, and the levels of inflammatory markers were almost normal. Therefore, we did not supplement the patient's treatment regimen with MTZ or CLDM. Furthermore, carbapenems have broad-spectrum activity against gram-positive, gram-negative, and anaerobic bacteria. Taken together, these findings suggest that clinicians might be able to treat patients suspected of carrying LS with carbapenems alone.

Septicemic illness caused by *Fusobacterium necrophorum*, called as necrobacillosis (3, 26), arises from not only pharynx, but also the oral cavity, the gastrointestinal tract and the female genital tract (6). There are a few cases of necrobacillosis with no clear sources (3, 26). Nozawa et al. reported a case of liver abscess infected with *Fusobacterium necrophorum* without pharyngeal infections or IJV thrombosis (27). Furthermore, according to Nohrstrom et al., necro-

bacillosis may be accompanied by abscesses without any apparent venous thrombosis (28). Therefore, when a patient presents with any abscesses of unknown origin, we clinicians should also take necrobacillosis into consideration and treat the patient with the appropriate antibiotics despite the lack of pharyngitis or venous thrombosis.

Conclusion

We report a case of LS with liver abscess as the sole septic metastasis. DRPM was effective in treating the pathologic features of this condition including liver abscesses. LS is a rare disease but it may be fatal without prompt and appropriate treatment. LS should be taken into consideration when examining a patient with septic illness and liver abscess after pharyngitis despite the lack of common complications such as IJV thrombophlebitis or pulmonary lesions. In addition, monotherapy with carbapenems may be effective in treating LS.

The authors state that they have no Conflict of Interest (COI).

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