

Original Article

Lemierre's Syndrome Followed by Acute Respiratory Distress Syndrome Successfully Rescued by Antibiotics and Hemoperfusion with Polymyxin B-Immobilized Fiber

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SUMMARY: Lemierre's syndrome is characterized by a primary oropharyngeal infection in a young healthy person who subsequently develops septic thrombophlebitis of the internal jugular vein and metastatic abscesses. We here report an uncommonly severe case of Lemierre's syndrome with acute respiratory distress syndrome (ARDS), in which polymyxin B-immobilized fiber (PMX) was used as supportive therapy. A 30-year-old, previously healthy man presented with sore throat, fever, rigor, and dyspnea. Chest computed tomography scan revealed multiple bilateral peripheral pulmonary nodules with small bilateral pleural effusions. The patient's condition rapidly deteriorated into ARDS after admission. Intubation followed by mechanical ventilation was required, and hemoperfusion with PMX was useful in alleviating the patient's condition. Isolation of *Fusobacterium necrophorum* from the blood culture and the contrast-enhanced scan revealed thrombosis and thrombophlebitis in the left internal jugular vein. The patient was diagnosed with Lemierre's syndrome, and an alternative treatment regimen with prolonged administration of ampicillin, clindamycin, and metronidazole resulted in improvement of the patient's respiratory function and general condition. Our case indicated that PMX might be an effective supportive therapy in severe cases of Lemierre's syndrome with ARDS that possessed no indication of surgical interventions.

INTRODUCTION

In 1936, Andre Lemierre reported 20 cases of thrombophlebitis of the internal jugular vein (IJV) with septic emboli (1). Recent judicious use of antibiotics has allowed this infection to resurface as a rare disease in clinical practice. A Danish retrospective study found an incidence of ~1 case per million per year (2). Lemierre's syndrome affects healthy adolescents and young adults with tonsillopharyngitis, otitis media, mastoiditis, or sinusitis (3). *Fusobacterium necrophorum* is a non-motile, pleomorphic, anaerobic Gram-negative rod that is reported to cause necrotic infections in wild and domestic animals (4,5) as well as in patients with Lemierre's syndrome. *F. necrophorum* spreads into the peritonsillar tissue, and invades the IJV, from which the infection metastasizes via the blood to the lungs, liver, kidneys, joints, bones, and meninges (6). It has been suggested that a reduced host defense in the pharyngeal mucosa due to viral or bacterial pharyngitis weakening the mucosal barrier may play a role in predisposing a patient to this syndrome (4,7,8). Here we report a severe and rare case of Lemierre's syndrome developed acute respiratory distress syndrome (ARDS). The patient was successfully rescued with a combination of the appropriate antibiotics and hemoperfusion with polymyxin B-immobilized fiber (PMX).

PATIENT AND LABORATORY INFORMATION

A 30-year-old man presented in the emergency room with a 5-day history of sore throat, high fever, and chest pain; a chest radiograph (CXR) and electrocardiogram performed at that time revealed no signs of pneumonia, pleuritis, or pericarditis. Two days later, he returned to the hospital due to deterioration of his symptoms, along with the development of shortness of breath. The patient was admitted to the hospital for further evaluation and immediate medical care. CXR examination revealed bilateral patchy opacities in the lungs. The patient's past medical and surgical history was unremarkable.

On physical examination, the patient was found to be lethargic, though well nourished and alert. His temperature was 40.4°C; blood pressure, 123/40 mmHg; pulse, 133 beats/min; respiratory rate, 40 breaths/min; and oxygen saturation, 90% while breathing room air. The patient's oropharynx was dry, and left tonsillar erythema and swelling without exudate was seen. Mandibular lymphadenopathy was evident on the left side, accompanied by tenderness and warmth. Auscultation revealed no rale in his chest. Cardiovascular examination was normal except for tachycardia, and no murmurs, rubs, or gallops were detected. Abdominal and neurological examinations were unremarkable, and the patient had no rash or petechiae.

Table 1 shows the laboratory findings. Elevation of the leukocyte count and C-reactive protein (CRP), as well as thrombocytopenia, were observed. Blood chemical tests demonstrated mild liver dysfunction and severe renal dysfunction. *Legionella pneumophila* and *Streptococcus pneumoniae* antigen tests in the urine were negative. Serum antibody titers

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Table 1. Laboratory findings on admission

Leukocyte	11,690/ μ l	Na	130 mEq/l
Sg.	95.5%	K	3.2 mEq/l
Ly.	3.3%	Cl	92 mEq/l
Mo.	1.0%	BUN	83.4 mg/dl
Eo.	0.1%	Cre	4.0 mg/dl
Ba.	0.1%	TP	6.0 g/dl
Erythrocyte	$453 \times 10^4/\mu$ l	T.bil	2.7 mg/dl
Hb	13.8 g/dl	AST	61 IU/l
Plt	$3.9 \times 10^4/\mu$ l	ALT	38 IU/l
FDP	19.41 μ g/ml	LDH	413 IU/l
Fibrinogen	999 mg/dl	CRP	30.0 mg/dl
PT (%)	88%		
APTT	30.1 Sec		
Serum endotoxin level	6.4 pg/ml		

Sg, segmented form; Ly, lymphocyte; Mo, monocyte; Eo, eosinophil; Ba, basophil; Hb, hemoglobin; Plt, platelet; FDP, fibrin degradation product; PT, prothrombin time; APTT, activated partial thromboplastin time; BUN, blood urea nitrogen; Cre, serum creatinine; TP, total protein; T.bil, total bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; CRP, C-reactive protein.

to *Mycoplasma pneumoniae* and *Chlamydothila pneumoniae* were not elevated.

Computed tomography (CT) scan of the patient's chest revealed multiple nodular opacities in both lung fields accompanied by a small amount of bilateral pleural effusion (Figure 1). The patient was diagnosed with tonsillitis, septic emboli in the lung due to bacterial sepsis, and disseminated intravascular coagulation. Intravenous meropenem at 1.0 g/day and clindamycin at 1.2 g/day were initiated after sputum, blood, and urine specimens had been collected for culture.

In spite of the antimicrobial treatment, the patient's high fever persisted, and his CRP value remained high. CXR examination on day 4 revealed a spreading of the diffuse bilateral lung shadows, and an increase in pleural effusion (Figure 2). Arterial blood gas analysis (6 liter/min oxygen inhalation) demonstrated an oxygen tension of 65.4 mmHg, carbon dioxide of 38.3 mmHg, and pH of 7.474. Multiorgan failure was observed with a Sequential Organ Failure Assessment score of 15, and a poor prognosis was predicted. The patient met the criteria for ARDS proposed at the American-European Consensus Conference on ARDS (9), and mechanical ventilation was initiated to mitigate the condition. The PaO₂/FiO₂ ratio was 96 mmHg with the patient on the respirator. Due to elevated serum endotoxin levels detected upon admission (6.4 pg/ml), and the development of renal dysfunction during the course of hospitalization, both continuous veno-venous hemodiafiltration (CVVHDF) and polymyxin B-immobilized fiber (PMX) were started on hospital day 4 followed by CVVHDF alone on days 5-10. The patient recovered from septic shock after a single course of PMX therapy on day 4.

On hospital day 6, the results of the blood culture test indicated the presence of *F. necrophorum*, and a diagnosis of Lemierre's syndrome, characterized by sepsis accompanied by thrombophlebitis of the IJV, was suspected. Contrast CT of the neck revealed a hypodense filling defect (Figure 3) suggestive of a thrombus in the left IJV, and an adjacent peritonsillar abscess. Although surgical treatment (e.g., vascular surgical intervention or drainage of the abscess) was considered, such management was not indicated due to the patient's extremely severe disease status. The antibiotic regimen was changed from meropenem to intravenous ampicillin



Fig. 1. CT scan on admission showing multiple bilateral peripheral pulmonary nodules with central cavitation, and small bilateral pleural effusion.

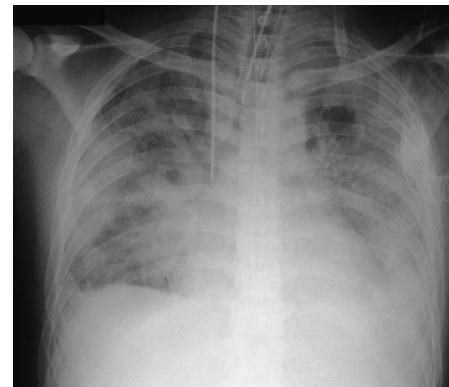


Fig. 2. On hospital day 4, chest X-ray revealed bilateral diffuse pulmonary infiltrations indicative of acute respiratory distress syndrome.

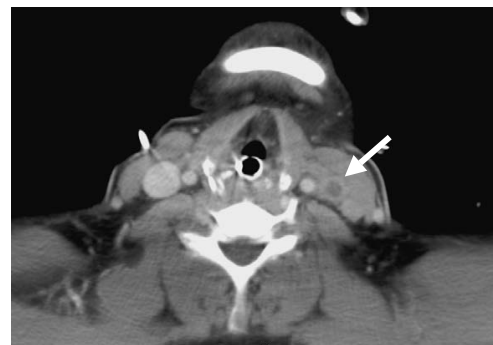


Fig. 3. On hospital day 6, contrast-enhanced CT of the neck demonstrated a hypo-attenuating intraluminal thrombus (arrow head) within the left internal jugular vein.

at 12 g/day, intravenous clindamycin at 2.4 g/day, and oral metronidazole at 1.5 g/day, according to the recommended treatment in the literature (4). Anticoagulation therapy with heparin at 10,000 U/day was also initiated. Drug susceptibility testing of the isolated strain showed that the minimal inhibitory concentrations (MICs) of penicillin G, ampicillin, cefmetazole, imipenem-cilastatin, and clindamycin were 0.06, 0.06, 0.5, 0.12, and 0.06 μ g/ml, respectively. Over the following 14 days, the patient recovered gradually from respiratory and renal failure, and the laboratory findings revealed a return to normal levels of the serum bilirubin and platelet count, without further platelet transfusions. The clinical course is summarized in Figure 4. CT scan of the neck using contrast material on hospital day 37 demonstrated that the left IJV was not discernable, suggesting that the IJV did not recanalize

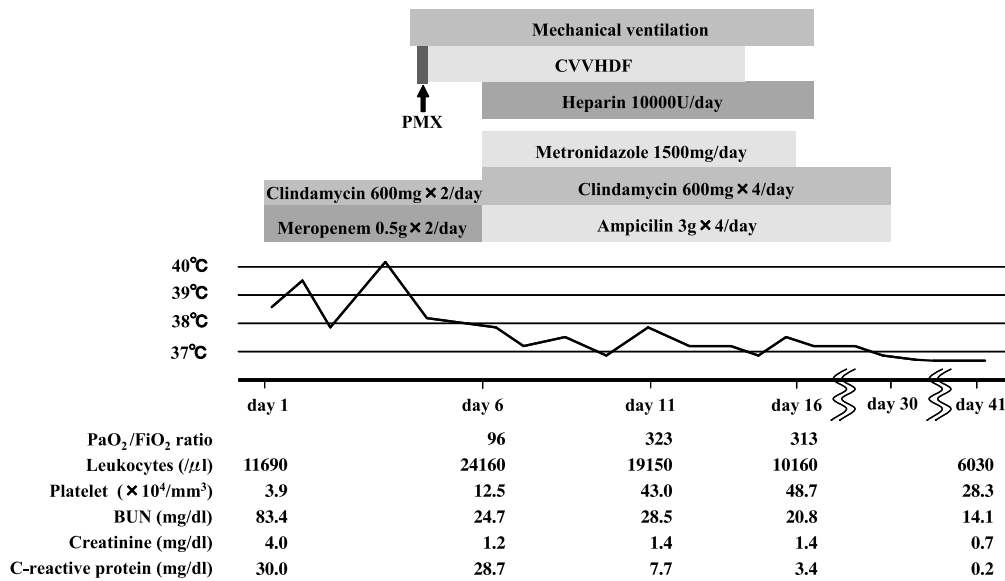


Fig. 4. Clinical course of the case. *Fusobacterium necrophorum* was isolated from blood on day 6. The patient recovered gradually from respiratory and renal failure and laboratory findings revealed a return to normal levels of serum urea nitrogen and creatinine. PMX, polymyxin B-immobilized fiber therapy; CVVHDF, continuous veno-venous hemodiafiltration; BUN, blood urea nitrogen.

after resolution of infection in this patient, as has also been reported previously in other cases (10). There were no signs of a residual peritonsillar abscess. The patient became symptom-free and was discharged on hospital day 44. No recurrence was observed after discharge.

DISCUSSION

We experienced an uncommonly severe case of Lemierre's syndrome with ARDS caused by septicemia of *F. necrophorum*. To the best of our knowledge, this is the second case report of Lemierre's syndrome with acute respiratory failure (11) and the first report in which PMX was used as a supportive therapy.

The current patient did not receive antibiotics until 7 days after the onset of symptoms, and this delay was most likely a contributing factor to the further deterioration to ARDS, although the underlying mechanism of the rapid progression of the disease in this patient is not known. Since the disease status of the patient was too severe for him to receive surgical treatment, the administration of suitable antibiotics and supportive therapy were crucial. The *F. necrophorum* isolated in this case was sensitive to all drugs, including imipenem-cilastatin and clindamycin. The administration of meropenem and clindamycin did not induce any remarkable effects within the first 6 days of administration. It remains possible that the concentrations of these drugs were not sufficiently high at the abscess lesion site, due to the relatively low doses of drug administered. Even antibiotics that are effective against causative microorganisms in vitro may not always be effective in such deep-tissue infections. Surgical drainage could be the most effective and reliable treatment in patients with Lemierre's syndrome, though the severely ill status of the patient limited its indication in this case.

Although Lemierre's syndrome is rare, when patients experience persistent high fever and respiratory symptoms such as dyspnea, chest pain, and cough following parapharyngeal infections, primary care physicians should immediately perform CT scans of the neck and head, and blood culture tests

prior to the administration of antibiotics, in order to ensure the early diagnosis of this often forgotten disease. Accurate diagnosis followed by the appropriate use of antibiotics or drainage of the abscess in these patients may avoid the potentially more serious consequences of Lemierre's syndrome.

Like other Gram-negative bacteria, *F. necrophorum* releases lipopolysaccharide (12), which most likely causes ARDS, as evidenced by the elevated serum endotoxin levels observed in our patient. PMX has been reported to be effective at ameliorating the severe conditions of patients with septicemia (13,14), and recent studies have demonstrated that PMX improves the PaO₂/FiO₂ ratio (15) and suppresses the function of activated monocytes in the peripheral blood of ARDS patients (16). Our case indicates that PMX may be an effective supportive therapy in cases of severe Lemierre's syndrome with ARDS that lack surgical indication or are refractory to antimicrobial treatment.

In conclusion, this is the first report of Lemierre's syndrome with ARDS being successfully treated by the appropriate use of antibiotics and PMX. The delay in diagnosis in this case most likely contributed to the severe complications. Thus, early diagnosis followed by proper management, including the appropriate use of antibiotics and surgical intervention, are essential for obtaining better outcomes for patients with this often forgotten disease.

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