Lemierre’s Syndrome Associated with Periodontal Injury-derived Odontogenic Infection that Did Not Respond to Meropenem

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Abstract

A 33-year-old previously healthy man injured his gums and subsequently developed dyspnea and fever. A chest X-ray showed nodules and infiltrates in both lungs, and the patient was initially diagnosed with pneumonia and administered meropenem hydrate, although his symptoms did not improve. A blood culture identified Fusobacterium necrophorum, and thrombophlebitis in the internal jugular vein of the neck was observed on computed tomography and ultrasound scans. We replaced the meropenem with clindamycin, sulbactam/ampicillin and metronidazole, and the patient’s symptoms improved.

Key words: Lemierre’s syndrome, oral injury, sepsis, Fusobacterium, thrombophlebitis, meropenem

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Introduction

Lemierre’s syndrome (LS) was first described by Courmont and Cade in 1900 and was well defined by Lemierre in 1936 (1). LS is characterized by anaerobic bacterial infections of the head and neck, with subsequent thrombophlebitis in the internal jugular vein (IJV) and the development of metastatic infections, especially in the lungs, joints, liver, brain, kidneys and various other organs. Interestingly, LS primarily occurs in previously healthy adolescents and young adults (mean age: 20 years).

Fusobacterium necrophorum is the most common etiological agent of LS, detected in more than 80% of recently reported cases (2). In latter reports, other oral flora, such as Peptostreptococcus, Streptococcus and Bacteroides species, were less common. The most frequent primary infection encountered in patients with LS is tonsillitis (accounting for approximately 90% of cases), with odontogenic infections in less than 2% of cases (3).

Antibiotic treatment, including carbapenems [e.g., meropenem (MEPM), imipenem, etc.], tigecycline, a combination of penicillin and a β-lactamase (BL) inhibitor (sulbactam/ampicillin sodium; SBT/ABPC) or clindamycin (CLDM), has been shown to be effective against LS.

We herein describe a case in which LS associated with an injury-derived odontogenic infection did not respond to MEPM. We successfully treated the patient’s LS with a combination of CLDM, SBT/ABPC and metronidazole (MTZ).

Case Report

A 33-year-old previously healthy male Japanese soldier cut his gum in the region between his right maxillary molars and premolars while eating an oyster (nine days before admission). Three days later, he developed swelling and pain over the right mandible and sternocleidomastoid muscle with a slight fever and therefore consulted a dentist. He was subsequently diagnosed with right maxillary gingival swelling and prescribed cefteram pivoxil (100 mg, three times daily). Three days before admission (six days after sustaining the injury), he developed a cough, dyspnea, purulent sputum and 40°C fever and thus visited a nearby hospital, where a chest X-ray revealed nodules and infiltrates in both lungs. He was initially diagnosed with pneumonia and transferred to JSDF Central Hospital.

A physical examination showed that the patient was 166
cm tall and weighed 76.3 kg, with a body temperature of 39.4°C. An examination of his vital signs demonstrated tachypnea (respiratory rate: 39/min), tachycardia (pulse rate: 115/min) and an oxygen saturation of 94% under oxygen supplementation via a 2-liter nasal cannula. In addition, he exhibited yellowing of the bulbar conjunctiva, right maxillary gingival swelling and bilateral coarse crackles.

A laboratory examination disclosed leukocytosis (white blood cells: 20,740/mm³, with 90% neutrophils), thrombocytopenia (platelet count: 9,800/mm³), a serum C-reactive protein level of 29.46 mg/dL, serum procalcitonin level of 11.43 ng/mL, jaundice (serum total bilirubin level: 7.96 mg/dL), serum creatinine level of 2.39 mg/dL, serum blood urea nitrogen level: 45 mg/dL, serum creatinine level: 2.39 mg/dL). An arterial blood gas analysis revealed hypoxia and respiratory alkalosis (pH: 7.46; partial CO₂ pressure: 32.3 mmHg; partial O₂ pressure: 74.0 mmHg; bicarbonate concentration: 22.8 mEq/L). In addition, a chest X-ray showed that the infiltrates in the lungs had increased in size, and a chest computed tomography (CT) scan detected multiple nodules (Fig. 1) in both lungs. Moreover, abdominal CT and ultrasonography demonstrated hepatomegaly, splenomegaly and renal swelling.

As we initially suspected pneumonia, we performed blood and sputum cultures and rapid serological tests and administered MEPM hydrate (0.3 g, four times daily) intravenously and azithromycin (AZM; 0.5 g, once daily) orally. However, on hospital day 4, a physical examination (which demonstrated a persistent fever and tachycardia) and laboratory studies (which revealed leukocytosis, inflammatory reactions and jaundice) did not show any improvements in the patient’s condition. Although serological tests produced negative results for Streptococcus pneumoniae and Legionella pneumophila, blood cultures identified Fusobacterium necrophorum and Doppler ultrasonography depicted right IJV thrombosis. Therefore, we diagnosed the patient with LS. We decided that the MEPM had not been effective and subsequently replaced it with CLDM (600 mg, three times daily, i.v.) and SBT/ABPC (1.5 g, four times daily, from the fifth day of hospitalization, i.v.). However, the patient’s symptoms did not noticeably improve. Hence, we added MTZ (1.0 g, once daily, from the sixth day of hospitalization, p.o.). On hospital day 9, a physical examination demonstrated that the patient’s fever and tachypnea had gradually improved, and a laboratory examination showed that the leukocytosis, thrombocytopenia, jaundice and renal failure had been ameliorated. However, neck CT revealed a 10-cm-long thrombotic segment in the right IJV (Fig. 2, 3).

A susceptibility test based on the E-test method indicated that the causative bacterium in this case was resistant to AZM and MEPM; however, its susceptibility to other antibiotics was not assessed. Therefore, the disk diffusion method was applied as an auxiliary diagnostic technique to obtain reference values. As a result, the zones of inhibition for CLDM [≥21 mm (S), 15 to 20 mm (I) and ≤14 mm (R)], SBT/ABPC [≥15 mm (S), 12 to 14 mm (I) and ≤13 mm (R)] and MEPM [≥16 mm (S), 14 to 15 mm (I) and ≤13 mm (R)] had diameters of 26, 21 and 16 mm, respectively. Furthermore, the broth microdilution method demonstrated that the causative bacterium in this case was susceptible to CLDM, although its susceptibility to MEPM and SBT/ABPC was not assessed (Table 1).

On hospital day 25, Doppler ultrasonography indicated that the thrombosis in the right IJV had reduced in size, and a chest X-ray showed that the infiltrates and nodules in the lungs had improved. On hospital day 30, the antibiotic regimen was switched to CLDM (300 mg, three times daily, p.o.) and SBT/ABPC (375 mg, three times daily, p.o.). On hospital day 43, neck CT demonstrated that the IJV thrombosis had disappeared, chest CT showed that the lung nodules and infiltrates had reduced in size and abdominal CT indicated that the hepatomegaly, splenomegaly and renal swelling had each improved. The patient was discharged on hospital day 47. At three months after discharge, the thrombosis had not relapsed.

We conducted a full review of this case. Indeed, this patient’s symptoms, particularly his general condition, wors-
Figure 2. Neck CT and IVJ ultrasound findings. IVJ ultrasound (a colored Doppler test) did not detect any blood flow in the right jugular vein (arrows) (A). Neck CT demonstrated a hypointense lesion in the right jugular vein (circle) (B). These findings were indicative of thrombophlebitis of the right jugular vein.

Figure 3. Clinical course (day 1-13).

Discussion

In the pre-antibiotic era, LS was a notorious disease with a high mortality rate; however, its incidence decreased after the introduction of antibiotics. Hence, it has since been referred to as a forgotten disease (4). However, a recent sys-
In particular, we should have suspected LS due to periodontal injury-derived odontogenic infection, a history of oral infection and the detection of multiple diagnostic criteria for LS in healthy young men include sepsis, and multiple blood cultures. Therefore, the diagnosis of LS is often delayed. The patients’ symptoms improved after the other antibiotics were added or used to replace MEPM; therefore, MEPM alone is considered to be insufficient to treat LS.

In this case, the causative F. necrophorum was found to be more resistant to MEPM than MTZ according to the disk diffusion, E-test and broth microdilution methods; however, it was susceptible to CLDM. The patients’ symptoms did not result in any improvements in the patient’s fever or dyspnea. It was not until neck CT and ultrasonography were performed after the patient developed a fever.

Blood culture tests for F. necrophorum take time, and neck CT and ultrasonography are often conducted after the detection of F. necrophorum. Therefore, the diagnosis of LS is often delayed. The diagnostic criteria for LS in healthy young men include sepsis, a history of oral infection and the detection of multiple lung nodules on a chest X-ray. If these findings had been observed, the present patient could have been diagnosed earlier using neck CT and ultrasonography without the need for a blood culture test. In particular, we should have suspected LS based on the patient’s history and performed appropriate examinations to obtain an early diagnosis. In cases of LS, it is important to obtain a definitive diagnosis as soon as possible.

As for the antibiotics used to treat LS, CLDM, penicillin, carbapenems or a combination of penicillin and a βL inhibitor are usually employed (6). Recently, MEPM has been administered in many cases. In the current case, the patient’s fever and dyspnea worsened and did not respond to treatment with MEPM, and the causative F. necrophorum was found to be resistant to MEPM on a susceptibility test. A previous report of dental infection-associated LS detected F. necrophorum, Streptococcus, and Bacteroides species resistant to MEPM (7).

We researched cases of LS in which MEPM was administered (8-30). Of the 23 cases found in the literature, four patients were treated with MEPM alone, one of whom died. In the other 19 cases, other antibiotics were added or administered instead of MEPM after blood cultures showed F. necrophorum (or other anaerobic bacteria) or LS was diagnosed based on CT and/or ultrasound findings. In 15 of these cases, other antibiotics were added to MEPM, with the most common being CLDM and MTZ. In the remaining four cases, MEPM was replaced with SBT/ABPC, MTZ, penicillin G and/or CLDM (Table 2). In these 19 cases, the patients’ symptoms improved after the other antibiotics were added or used to replace MEPM; therefore, MEPM alone is considered to be insufficient to treat LS.

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>E-test method</th>
<th>The disk diffusion method (reference)</th>
<th>Broth microdilution method</th>
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<tr>
<td>MEPM*</td>
<td>Resistant</td>
<td>16 mm</td>
<td>Restricted</td>
</tr>
<tr>
<td>AZM*</td>
<td>Resistant</td>
<td>0 mm</td>
<td>Restricted</td>
</tr>
<tr>
<td>CLDM*</td>
<td>Resistant</td>
<td>26 mm</td>
<td>Susceptible</td>
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<tr>
<td>SBT/ABPC*</td>
<td></td>
<td>21 mm</td>
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<tr>
<td>PCG</td>
<td></td>
<td>15 mm</td>
<td>Restricted</td>
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<tr>
<td>PIPC</td>
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<td>26 mm</td>
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<td>VCM</td>
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The E-test and disk diffusion methods were performed at our hospital, whereas the broth microdilution method was performed by IBM. In the disk diffusion method, which was performed as an auxiliary diagnostic method, we estimated the diameters of the zones of inhibition for each antibiotic (which were used as reference values).

*The antibiotics administered in this case.

The above results suggest that CLDM and SBT/ABPC were more effective than MEPM or AZM.


Table 1. Antibiotic Sensitivity of F. necrophorum.
The authors state that they have no Conflict of Interest (COI).

not improve after MEPM treatment and we thus replaced the MEPM with CLDM, SBT/ABPC and MTZ. As a result, his symptoms improved and he was discharged within approximately six weeks. Hence, we believe the use of MEPM alone to treat LS to be inappropriate. If LS is suspected in a patient with habitual toothpick usage, J Microbiol Immunol Infect 46: 237-240, 2013.


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