Lemierre's Syndrome: *Porphyromonas asaccharolytica* as a Putative Pathogen

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Abstract

A case of Lemierre's syndrome is reported in which metastatic abscesses resulted from septic thrombophlebitis of the internal jugular vein secondary to bacterial pharyngitis. A 32-year-old male suffering from a painful left-sided neck mass, sore throat, and fever was admitted to our hospital. Computed tomography revealed thrombosis of the left internal jugular vein, septic pulmonary emboli, and a liver abscess. Blood culture showed *Porphyromonas asaccharolytica*. Although empyema occurred transiently during the treatment, the patient recovered following prolonged antimicrobial therapy. Although *Fusobacterium* species are a well-known cause of Lemierre's syndrome, cases in whom *Porphyromonas* species was isolated have scarcely been reported. Moreover, case reports from Japan have been few.

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Key words: Lemierre's syndrome, thrombophlebitis, *Fusobacterium*, *Porphyromonas*

Introduction

Internal jugular vein thrombosis rarely causes painful neck masses. In 1936, Lemierre characterized and reported a distinctive syndrome of postanginal sepsis and internal jugular vein septic thrombosis (1). The following criteria for Lemierre's syndrome are generally accepted: 1) anaerobic primary infection in the oropharynx, 2) subsequent septicemia demonstrated by at least one positive blood culture, 3) evidence of thrombophlebitis of the internal jugular vein, 4) metastatic infections at one or more distant sites (2, 3). The syndrome has a propensity to strike previously healthy teen-

agers and young adults. Initial symptoms of the syndrome are mainly nonspecific pain and swelling over the sternocleidomastoid muscle. The time of onset from the initial infection to the development of septicemia is typically 3 to 10 days. Septic embolization causes metastatic abscesses commonly in the lungs and less commonly in the large joints and the liver. In recent years, with widespread use of antibiotics to treat oral infections, this syndrome has become uncommon. Therefore, early diagnosis and treatment with effective antibiotic regimen can significantly reduce mortality and morbidity.

Over the past two decades, occasional case reports and literature reviews pertaining to Lemierre's syndrome have been published. The infection is caused mostly by *Fusobacterium necrophorum* and less commonly by other anaerobic organisms. However, there have been only a few case reports of the syndrome in Japan and only one case associated with *Porphyromonas* (4, 5). We describe a case with the classic clinical presentation and findings characteristic of Lemierre's syndrome. Isolates of *P. asaccharolytica* but not *Fusobacterium* were cultured from the patient's blood.

Case Report

A 32-year-old male with no significant past medical history presented to our hospital with a 4-day history of fever, sore throat, arthralgia, and neck pain restricting neck movements. Symptomatic treatment had been prescribed but there had been little response. Upon admission, he was febrile (39.5°C) and tachycardic with tender left cervical lymphadenopathy. On physical examination, a painful neck mass on the left side was observed. The mass extended to the upper cervical and parieto-occipital regions. Typical rales were heard in the middle field of the right lung. Laboratory tests showed an increased high-sensitivity C-reactive protein (CRP) level of 21.32 mg/dl and neutrophilia (91.7%, white blood cell count; 6,830/ μ l). Platelet count was 6.0×10^4 / μ l.

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Figure 1. Contrast-enhanced CT image of cervical region demonstrating enlargement of left internal jugular vein. A hypodense lesion can be seen (arrows), which is thought to have occurred because of thrombosis of the vein. The left external jugular vein and right internal and external jugular veins appeared to be normal.

Coagulation test results were as follows: activated partial thromboplastin time, 38.1 seconds (control 27.5 seconds); prothrombin time, 62%; fibrinogen, 760 mg/dl; D-dimer, 7.5 μ g/ml; FDP, 15.4 μ g/ml; and antithrombin III, 99%. On the first day of admission, blood culture was examined in culture bottles, BacT/ALERT SA and SN (Biomérieux, Inc., Lyon, France), and the patient was treated with sulbactam-cefoperazone (4 g, 2 $\times$) and meropenem (2 g, 2 $\times$). Because of the beginning of antimicrobial therapy, no more blood culture assays were performed. Chest radiograph demonstrated bilateral patchy infiltrates. Computed tomography (CT) of the neck revealed a filling defect of the left internal jugular vein consistent with thrombosis and there were abscess-suspected lesions in the parapharyngeal area (Fig. 1). Computed tomography (CT) of the chest demonstrated round opacities of both lungs and a small cavitory lesion was seen on the right-sided opacity in Fig. 2. On abdominal CT, an abscess-like low density area was found in the gallbladder bed of the liver (Fig. 3). According to these findings, a provisional clinical diagnosis of Lemierre's syndrome with septic disseminated intravascular coagulation (DIC) was made. After the diagnosis, intravenous administration of clindamycin (2.4 g, 4 $\times$), meropenem (2 g, 2 $\times$), and teicoplanin (400–800 mg, 1–2 $\times$) was started. Subsequently, inflam-

A

B

Figure 2. Chest CT image demonstrating round or patchy opacities (A and B, arrows) in the right lung consistent with septic emboli. Small cavitory lesions can be seen on the opacities.

matory markers gradually decreased and cultures of blood drawn at admission were positive for *P. asaccharolytica* by Rapid Ana II testing (Remel, Inc., Lenexa, KS) which was sensitive to ongoing antibiotics. Isolated *P. asaccharolytica* was sensitive to ampicillin (ABPC), imipenem (IPM), cefazolin (CEZ), cefaclor (CCL), minocycline (MINO), chloramphenicol (CP), erythromycin (EM), clindamycin (CLDM), flomoxef (FMOX), cefmenoxime (CMX), cefminox (CMNX), cefdinir (CFDN), latamoxef (LMOX), levofloxacin (LVFX), fosfomycin (FOM), and azithromycin (AZM), and resistant to gentamycin (GM) and amikacin (AMK). Teicoplanin was administered for the possibility of additional infection, e.g., methicillin resistant *Staphylococcus aureus*. Treatment for DIC consisted of gabexate mesilate and danaparoid.

During the second week of the treatment, however, the patient experienced bilateral pleuritic chest pain. Chest radiography at this stage revealed bilateral pulmonary infiltrates

Figure 3. CT image of the upper abdomen revealed the presence of a low attenuation lesion in the liver (arrow).

with pleural effusion and CRP increased again (to 15.31 mg/dl). The effusion did not smell nasty and no bacteria were identified in effusion culture. The analysis of the effusion revealed empyema: cell count, $1 \times 10^4/\mu\text{l}$; specific gravity, 1.030; total protein, 4.5 mg/dl; and LDH, 1,220 U/l. Therefore, the antibiotics regimen was changed to clindamycin (2.4 g, 4 $\times$) and biapenem (1.2 g, 2 $\times$) to which the isolated *P. asaccharolytica* were also sensitive. These treatments proved effective, and after 3-week chemotherapy, CRP gradually decreased, ultimately returning to below detectable levels. On CT scans on day 34, there was no evidence of thrombosis, abscess, or inflammation of the neck, chest, or abdomen. Anticoagulation therapy was changed to oral administration of warfarin. The patient improved and was discharged on day 48.

Discussion

This patient presented symptoms that fit the generally accepted criteria for Lemierre's syndrome: occurrence in healthy children and young adults, previous oropharyngeal infection, septicemia following oropharyngeal infection, swelling and lateral neck tenderness, and metastatic abscesses of the lung and liver. *Fusobacterium* was not isolated from the patient's blood or other tissues, but *P. asaccharolytica* was isolated from blood culture. *F. necrophorum* and other *Fusobacterium* species have remained the most common pathogens in Lemierre's syndrome and accounted for over 90% of the cases in a recent review (2, 6, 7). Both *Fusobacterium* and *Porphyromonas* species belong to the family Bacteroidaceae, which are anaerobic gram-negative rods found as part of the indigenous flora of the oropharynx, gastrointestinal tract, and genitourinary tract (8). The anaerobic gram-negative bacteria show a similar susceptibility pattern to antimicrobial agents (8).

Parapharyngeal invasion by infiltrates and lymphatic or tonsillar venous are central to the development of Lemierre's syndrome. It is unclear why these pathogens become invasive subsequent to local infections. Organisms of the family of Bacteroidaceae are considered to be associated with thromboembolic phenomena. They release a lipopolysaccharide (LPS) component, which has strong biologic activity, and a lipid A moiety that has been implicated in the promotion of coagulation (6, 9). The coagulation mechanism is platelet-independent and does not require terminal components of complement. Therefore, once inflammation of the pharynx occurs, coagulation may be promoted, devitalized tissue with impaired blood supply may provide the anaerobic environment for bacterial proliferation, local defense may be compromised, and invasion by pharyngeal flora may be augmented. Furthermore, it is thought that proteolytic enzymes produced by the bacteria are associated with the spread of the infection.

The most common pathogen of Lemierre's syndrome, *F. necrophorum*, is a very virulent anaerobe that is peculiar in its ability to invade as a primary pathogen without the presence of serious underlying disease, and may cause severe infection (6). *F. necrophorum* infection may take part in the impairment of mucosal and cutaneous defense mechanisms because many of its extracellular products have been identified and presumably play a role in its spread into the tissues and bloodstream. It produces leukocidin, hemolysin, hemagglutinin, and lipase (6, 10–12). Leukocidin assists in the destruction of leukocytes, impairs leukocyte migration, and protects other facultative pathogens from phagocytosis. A possible role of hemolysin may be to aid in creating an anaerobic environment by lysing the erythrocytes and thereby reduce oxygen transport to the site of infection. Hemagglutinin causes platelet aggregation without lysis, and septic thrombus formation, thereby contributing to the establishment of a favorable anaerobic environment for growth of *F. necrophorum*. It has been suggested that phospholipase A and lysophospholipase are the components responsible for the hemolytic activity.

Only *P. asaccharolytica* was isolated from this patient; however, it is unclear whether this was truly the main pathogen present. First, *Porphyromonas* species are not as virulent as *F. necrophorum*. Second, in some cases no organism is isolated from blood cultures. Third, organisms most commonly isolated with *Fusobacterium* are anaerobic bacilli including *Porphyromonas* species (6, 10, 13). Lastly, within *Porphyromonas* species, *P. gingivalis* and *P. endodontalis* are encountered in the oral cavity (8). They are important pathogens in oral, dental, and bite infections, and may readily multiply in the head, neck, and lower respiratory tract. On the other hand, it is commonly accepted that *P. asaccharolytica* is prevalent in the urogenital and intestinal tracts and is important in infections arising in these regions (8).

A synergistic, pathogenic complex has been demonstrated between *Fusobacterium* species and other anaerobic bacteria in the formation of abscesses in animal models. The complex

facilitates the growth of *F. necrophorum* by lowering the oxygen tension and creating an anaerobic environment (10, 13, 14). Therefore, a similar synergistic relationship might occur between *F. necrophorum* and *P. asaccharolytica*, and this might play a role in the pathogenesis of Lemierre's syndrome in the present patient.

The course of Lemierre's syndrome is usually protracted because of continuing septic embolization. However, the role of anticoagulation therapy is controversial. Some reports do not recommend anticoagulation because early clot dissolution may promote the risk of extending the infection and the risk for emboli and hemorrhage (15–18). Others suggest that anticoagulation, by enhancing resolution of the source of septic embolization, may expedite quicker recovery from the thrombophlebitis (19–21). We added anticoagulation therapy with gabexate mesilate and danaparoid because the patient showed signs of DIC. We cannot appraise the clinical significance of the treatment and the routine use of anticoagulation therapy remains controversial.

Lemierre's syndrome will continue to occur mainly in children and young adults even in the modern antibiotic era. We hope that this report will heighten awareness and facilitate the diagnosis of Lemierre's syndrome.

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