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Case report

Bilateral parapneumonic empyema caused by *Fusobacterium necrophorum* infection in a healthy individual

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ABSTRACT

Pulmonary infection caused by *Fusobacterium necrophorum*, an obligate anaerobic gram-negative bacterium, most commonly occurs as a part of Lemierre's syndrome, i.e., pharyngotonsillitis complicated by septic thrombophlebitis of the internal jugular vein and secondary lung abscesses. A 51-year-old previously healthy man was admitted to our hospital with pleuritic right-sided chest pain. No sore throat, dysphagia, or neck pain was observed. Chest radiography and computed tomography (CT) revealed massive right pleural effusion and bilateral bronchopneumonia. Right thoracic drainage yielded purulent fluids, from which a pure culture of *F. necrophorum* was isolated. Blood culture and broad-range polymerase chain reaction for bacterial 16S ribosomal ribonucleic acid on blood samples were negative. CT scan showed no evidence of internal jugular vein thrombosis or peritonsillar abscess. The right thoracic tube was removed after the purulent fluids were no longer drained. Although the antibiotic treatment was continued with intravenous sulbactam/ampicillin, to which *F. necrophorum* was sensitive, left purulent pleural effusion emerged. The antibiotic was switched to clindamycin, cefazolin, cefotiam, and flomoxef. Although the left pleural effusion gradually decreased, the right purulent pleural fluid was reaccumulated. Thus, the patient underwent right-sided thoracoscopic decortication and debridement, followed by thoracic lavage through a chest tube with saline solution. After the surgery, the patient's condition improved, and no recurrence of pleural effusion was observed. This report presents the case of a previously healthy patient with bilateral parapneumonic empyema caused by *F. necrophorum*, without manifestations of pharyngotonsillitis, bacteremia, or Lemierre's syndrome. Extensive thoracic drainage, effective antibiotics, and timely surgical interventions are imperative.

Introduction

Fusobacterium is an obligate anaerobic gram-negative bacterium commonly found in the normal oral, gastrointestinal, and genital flora [1–3]. Fusobacterium infections, albeit rare, present with a wide clinical spectrum, ranging from local pharyngotonsillitis to life-threatening sepsis with metastatic infections in the brain, lungs, liver, joints, and heart valves [1–3]. The most isolated pathogens in Fusobacterium species are *Fusobacterium nucleatum* and *Fusobacterium necrophorum*. *F. nucleatum* is recently considered to be a common pathogen of empyema likely caused by bacterial spreading from periodontitis to the thoracic cavity [4]. In contrast, pulmonary infection by *F. necrophorum* most commonly occurs as a part of Lemierre's syndrome, that is, pharyngotonsillitis complicated by septic thrombophlebitis of the internal

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jugular vein, leading to secondary lung abscesses [5]. Thus, pulmonary infection caused by *F. necrophorum* is usually related to anteceding pharyngotonsillitis. We report a case of bilateral parapneumonic empyema due to *F. necrophorum* infection that affected a previously healthy patient without pharyngotonsillitis or Lemierre's syndrome.

Case

A 51-year-old male patient was admitted to our hospital with a 3-week history of pleuritic right-sided chest pain, cough, dyspnea, and subjective fever. No sore throat, dysphagia, or neck pain was observed. He was an active smoker (20 cigarettes per day for 30 years) and had a history of urinary infection at 2 years of age and recurrent herpes labialis over adulthood. The patient was otherwise healthy and enjoyed playing tennis before the onset of the current symptoms. He denied a history of aspiration, food regurgitation, or excessive alcohol intake. On physical examination, he had a fever (37.6 °C), heart rate of 106 bpm, blood pressure of 128/68 mmHg, and oxygen saturation of 94 % on a 2-L nasal cannula. No pharyngitis, tonsil enlargement, cervical adenopathy, or neck swelling was observed. An oral examination by a dentist identified periodontitis as mild. On auscultation, heart sounds were normal; however, breath sounds decreased over the right side of the chest. The laboratory tests revealed a white cell count of 50.2×10^9/L, with 95 % neutrophils, hemoglobin of 13.4 g/dL, and platelet count of 336×10^9/L. The C-reactive protein (CRP) was 364 mg/dL. Liver and kidney functions were normal. The human immunodeficiency virus (HIV) test result was negative. The urine pneumococcal and Legionella antigen test results were negative. Chest radiography and computed tomography (CT) revealed massive right pleural effusion and bronchopneumonia in the bilateral lower lobes (Fig. 1**A**–**E**).

The patient underwent right-sided needle thoracocentesis, by which purulent fluids were obtained, and was tentatively diagnosed with bilateral pneumonia complicated by right empyema. Empirical antibiotic therapy was initiated with intravenous sulbactam/ampicillin (3 g four times a day) according to the Japanese Association for Infection Japanese Society of Chemotherapy Guidelines to Clinical Management of Infectious Disease [6], after obtaining two sets of aerobic and anaerobic blood cultures from two different sites, which were eventually found to be negative (Fig. 2). The result of broad-range polymerase chain reaction (PCR) for bacterial 16S ribosomal ribonucleic acid (rRNA) on blood samples was also negative. A right thoracic tube was inserted, which drained 3130 mL of pleural fluid over 14 days of admission, and the fluid collection was drained to dryness. The pleural fluid yielded a pure anaerobic culture of *F. necrophorum*, which was sensitive to sulbactam/ampicillin (Table 1). The aerobic culture yielded no growth. Urine culture obtained on the day of admission was negative. Although *F. necrophorum* is a common pathogen in Lemierre's syndrome, CT scan showed no evidence of internal jugular vein thrombosis, peritonsillar or retropharyngeal abscess, or liver abscess. Brain CT and magnetic resonance imaging were not performed because the neurological findings of the patient were normal.

A follow-up contrast-enhanced CT scan on day 8 of admission revealed improvements in the bilateral pneumonia and a reduction in the right pleural effusion, whereas left pleural effusion emerged (Figs. 1**F**, 1**G**, and Fig. 2). Left-sided thoracocentesis yielded purulent-appearing pleural fluid, albeit negative for aerobic and anaerobic bacterial cultures, leading to our diagnosis of parapneumonic empyema, which affected both sides of the thoracic cavities. The patient refused to undergo left tube thoracostomy because the anteceding right tube thoracostomy was so painful. The right thoracic tube was removed on day 14 of admission when the purulent fluids were no longer drained. The initial antibiotic treatment with sulbactam/ampicillin was discontinued on day 16 of admission (Fig. 2) because of drug eruption and was switched to clindamycin (600 mg three times a day) based on the results of the antibiotic sensitivity test (Table 1). Thereafter, the antibiotic treatment was changed to cefazolin (2 g three times a day), cefotiam (2 g three times a day), and flomoxef (2 g twice a day) because the patient's body temperature and blood CRP levels remained high, although the left pleural effusion gradually decreased (Fig. 2). However, the right pleural fluid was reaccumulated 5 days after the removal of the right chest tube (Figs. 1**H**, 1**I**, and 2**)**. Thoracocentesis of the right side yielded purulent pleural fluid again, which contained 16S rRNA matching only *F. necrophorum* detected by broad-range PCR. The recurrence of Fusobacterium empyema was diagnosed, which was not improved despite continuous treatment with sensitive antibiotics (Fig. 2). Thus, the patient underwent right-sided thoracoscopic decortication and debridement on day 33 of admission, followed by thoracic lavage through a chest tube with saline solution for 7 postoperative

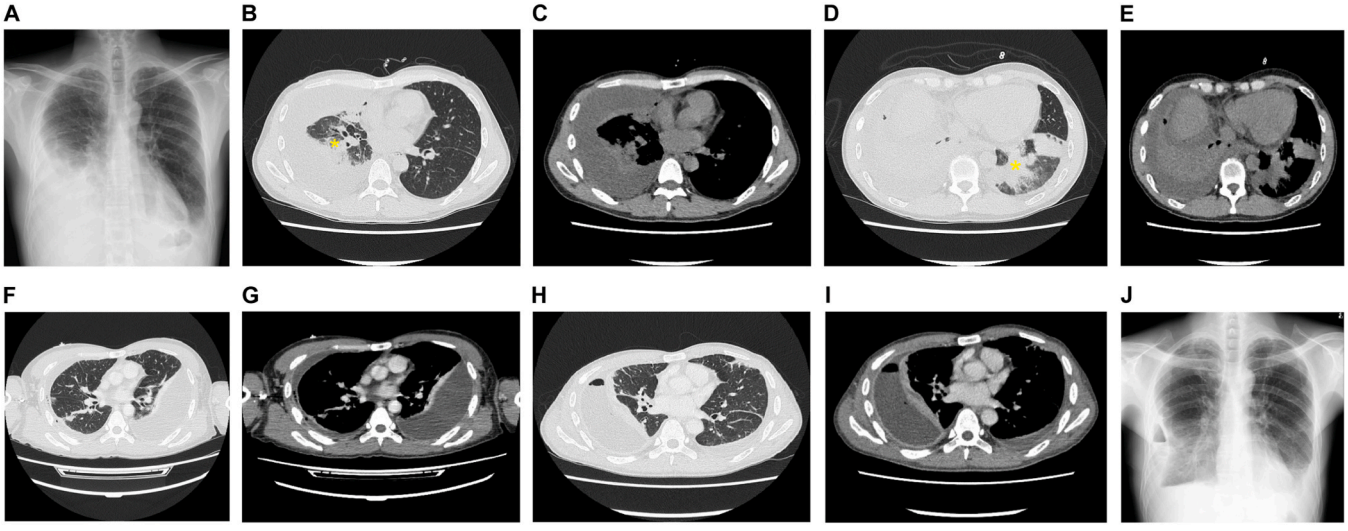

Fig. 1. Radiographic images of the chest. (**A**) Chest radiography on the day of admission shows massive right pleural effusion. (**B**–**E**) The lung window (**B** and **D**) and mediastinal (**C** and **E**) window images of chest plain computed tomography (CT) on the day of admission show massive right pleural effusion and bronchopneumonia (*) in the bilateral lower lobes. (**F** and **G**) The lung window (**F**) and mediastinal (**G**) window images of chest contrast-enhanced CT on day 8 of admission reveal improvements in the bilateral pneumonia and a reduction in the right pleural effusion, whereas left pleural effusion emerges. (**H** and **I**) The lung window (**H**) and mediastinal (**I**) window images of the chest plain CT on day 19 of admission show the reaccumulation of the right pleural fluid. (**J**) Chest radiography on the day of discharge shows no recurrence of pleural effusion.

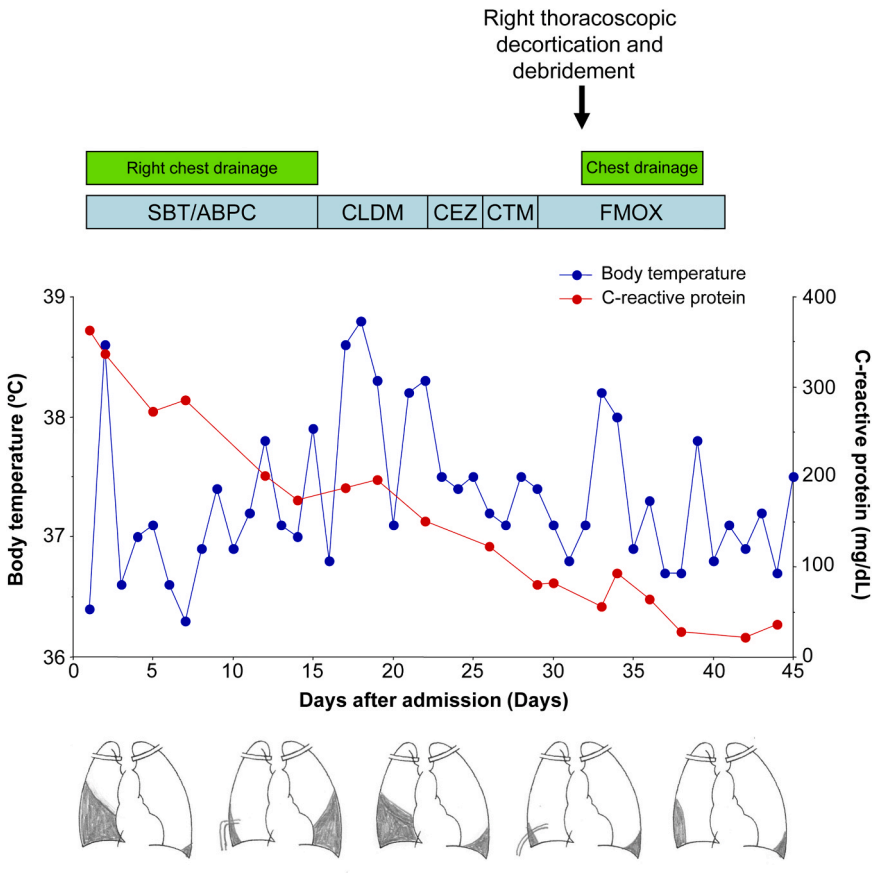

Fig. 2. Timeline of the patient's clinical course. SBT/ABPC, sulbactam/ampicillin (12 g/day); CLDM, clindamycin (1.8 g/day); CEZ, cefazolin (6 g/day); CTM, cefotiam, 4 g/day); FMOX, flomoxef (4 g/day).

Table 1
Results of the drug susceptibility test.

Drug	MIC (mg/L)	Interpretation
Sulbactam/ampicillin	≤ 0.1	Susceptible
Piperacillin	≤ 4	Susceptible
Tazobactam/piperacillin	≤ 4	Susceptible
Cefmetazole	≤ 2	Susceptible
Cefotaxime	≤ 2	Susceptible
Cefoperazone	≤ 2	Susceptible
Ceftriaxone	≤ 2	Susceptible
Cilastatin/imipenem	≤ 0.5	Susceptible
Meropenem	≤ 0.5	Susceptible
Tetracycline	≤ 0.5	Susceptible
Clindamycin	≤ 0.25	Susceptible
Ampicillin	≤ 0.25	Susceptible
Chloramphenicol	≤ 2	Susceptible
Moxifloxacin	0.5	Susceptible
Metronidazole	≤ 1	Susceptible

days. After the surgery, the patient's condition improved with reductions in the blood CRP levels. No recurrence of pleural effusion was observed (Fig. 1**J**; the patient was discharged 45 days after admission.

Discussion

Parapneumonic empyema rarely affects both thoracic cavities particularly in immunocompetent individuals. Our study showed that *F. necrophorum* infections can be involved in such a rare disease condition. Fusobacterium infections are uncommon; the annual incidence of Fusobacterium infections and bacteremia is reported to be 0.76–1.78 and 0.53–0.55 cases per 100,000 population, respectively [1–3]. Although *F. necrophorum* and *F. nucleatum*, the most frequently isolated species within this genus, affect males more commonly than females [1–3], a considerable disparity between ages is present. *F. necrophorum* infections are prevalent in healthy, young patients (a median age of 20–40 years), whereas *F. nucleatum* infections preferentially affect older individuals (a median age of 50 years) who have comorbidities, such as malignancy and hemodialysis [1–3]. In previous literature, most reported cases of *F. necrophorum* infection involved individuals aged < 48 of age [2]. In this context, our case is a unique elderly case of *F. necrophorum* infection that affected a patient aged > 50 years.

Pulmonary infection by *F. necrophorum* usually manifests as a part of Lemierre's syndrome, that is, pharyngotonsillitis complicated by thrombophlebitis of the jugular vein, which causes septic pulmonary embolism [7]. However, our case had no evidence of upper respiratory tract infection or jugular venous thrombophlebitis, and the results of anaerobic (and also aerobic) blood culture and broad-range PCR for the bacterial 16S rRNA on blood samples were negative. Furthermore, septic pulmonary emboli in Lemierre' syndrome are usually observed on CT images as multiple peripheral lung nodules with occasional cavitation [7]. However, such lung nodules were absent in this study, which, instead, showed the features of bronchopneumonia in the bilateral lung fields, characterized by infiltrates spreading through the bronchovascular bundles. Based on these findings, we propose that the pulmonary infection in our patient was due not to hematogenous but due to bronchogenic spread of the pathogen. Our patient had mild periodontitis; this could be the source of infection, extending to pneumonia via aspiration of saliva containing oral bacteria. However, aspiration pneumonia rarely occurs in healthy individuals such as our patient, who was an active amateur tennis player. He had no comorbidities and denied episodes of aspiration, vomiting, dysphagia, or gastrointestinal regurgitation, although we could not rule out silent aspiration without any

overt clinical symptoms. A possible explanation for the patient's atypical presentation is that his smoking habit irritated periodontitis [8]; additionally, it promoted direct inhalation of *F. necrophorum* during smoking. Thus, vaping of electronic cigarettes is acknowledged as an emerging risk factor for *F. necrophorum* pneumonia in adolescents [9]. Furthermore, smoking increases the risk and severity of respiratory tract infections by impairing immune cell antimicrobial functions and inducing microbial resistance to attack by immune cells [10]. Thus, smoking may contribute to severe presentation of *F. necrophorum* infection in our patient. Another possibility is that our patient had an unrecognized immunodeficiency. He had a history of urinary infection at the age of 2 years and recurrent herpes labialis over adulthood, suggesting an occult immune deficit, although his HIV test result was negative. We did not rule out the possibility that undelaying unrecognized immune deficiency could have led to the progressive nature of *F. necrophorum* pneumonia leading to empyema in our patient. Third, it is possible that *F. necrophorum* was a bystander in a polymicrobial pulmonary infection. However, we doubt this possibility because it was the only organism detected in the pleural fluid by bacterial culture and broad-range PCR for the bacterial 16S rRNA gene.

A systematic review of bacterial pathogens causing empyema ranks *Staphylococcus aureus* as the most frequent isolate (20.7 %), followed by *Viridans streptococci* (18.7 %), *Pseudomonas* species (17.6 %), *Enterobacteriaceae* species (11.9 %), and *Streptococcus pneumonia* (10.8 %) [11]. Until recently, Fusobacterium species have not been considered the major causative agent of empyema because anaerobes are difficult to culture. However, recent studies using the 16S rRNA gene PCR technique have identified the anaerobe *F. nucleatum* and aerobe *Streptococcus intermedius* (both commonly implicated in periodontitis) as the most common pathogens of empyema particularly in cases not associated with pneumonia [4,12]. In contrast, empyema due to *F. necrophorum* infection is extremely rare if Lemierre's syndrome is absent. To the best of our knowledge, only one study has reported a case of *F. necrophorum* infection, which presented as parapneumonic empyema in the absence of pharyngotonsillitis or Lemierre's syndrome [13].

Our patient had a recurrence of Fusobacterium empyema that occurred after removal of a chest tube, resisted antibody therapy, and eventually required thoracoscopic decortication and debridement. Fusobacterium is an obligate anaerobe that grows only under aerobic conditions. We suspect that the removal of the chest tube generated a closed anaerobic environment in the thoracic space, which promoted the regrowth of Fusobacterium. Chest tube drainage and more aggressive surgical drainage provide adequate oxygenation in the empyema cavity, which may facilitate effective antibiotic treatment for Fusobacterium infection.

Our patient refused early surgery for the right-sided empyema. Thus, the delay in surgery led to prolonged hospital stays. The standard initial medical treatment for empyema, comprising antibiotics and chest tube drainage, fails in approximately 30 % of patients [14]. According to the American Association for Thoracic Surgery consensus guidelines, fibrinopurulent (stage II) or organized (stage III) empyema requires surgical intervention [15]. A recent systematic review with meta-analysis revealed that when chest tube drainage is ineffective, surgical management, such as decortication and debridement, resulted in increased the likelihood of treatment success and shorter chest drain duration and hospital stays than intrapleural fibrinolysis [16]. Thus, the right-sided surgical decortication in our patient should have been performed earlier.

In contrast to the right empyema, the left empyema was cured only with antibiotics without thoracic drainage, which the patient refused. The left pleural effusion was purulent but negative for bacterial cultures probably because of previous administration of sulbactam/ampicillin. Broad-range PCR tests for the bacterial 16S rRNA gene were not performed for the left pleural effusion. Thus, we did not rule out the possibility that bacteria with different antibiotic sensitivities other than *F. necrophorum* caused left empyema.

In conclusion, severe parapneumonic empyema due to *F. necrophorum* infection can occur in an immunocompetent host, even in the absence of pharyngotonsillitis, bacteremia, or Lemierre's syndrome. Extensive thoracic drainage, effective antibiotics, and timely surgical intervention are imperative. Given its rarity, a keen awareness of this organism is required in an otherwise unexplained pleuropulmonary infection, which may affect healthy individuals.

CRediT authorship contribution statement

Rena Tamenaga: Writing – review & editing. **Reimi Mizushima:** Writing – review & editing. **Yukihisa Takeda:** Writing – review & editing. **Yusuke Watanabe:** Writing – review & editing. **Takehiko Tanaka:** Writing – review & editing. **Eiji Nakajima:** Writing – review & editing. **Hiroyuki Nakamura:** Writing – review & editing. **Kazutetsu Aoshiba:** Writing – review & editing, Writing – original draft, Supervision. **Taro Kufukihara:** Writing – original draft.

Authors contributions

All authors have made significant contributions to the planning, conduct, and reporting of the work described in this article. All authors have read and approved the submission of this final manuscript.

Ethical approval

This case report meets the standards of the Tokyo Medical University Ethics Committee.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper, The authors declare nothing to disclose.

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Declaration of interest

None.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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