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Case report

Unexpected etiology of a pleural empyema in a patient with chronic lymphocytic leukemia (CLL): *Capnocytophaga ochracea*

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ABSTRACT

Pleural effusions and empyemas caused by *Capnocytophaga* spp. are uncommon with few cases previously reported. Here, we present the case of a 62-year-old man with untreated chronic lymphocytic leukemia (CLL) complicated by a pleural empyema caused by *C. ochracea*. The route of acquisition was likely the result of aspiration of *C. ochracea* coupled with the immune defects associated with untreated CLL.

Introduction

Infectious pleural effusions and empyemas may be caused by a variety of etiologies, including bacteria, viruses, fungi, and parasites [1]. In patients with community-acquired infections, *Streptococcus* spp. and anaerobes are the most common bacterial etiologies, whereas hospital-acquired infections are more commonly caused by methicillin-resistant *Staphylococcus aureus* (MRSA) and Enterobacteriaceae. However, patient-specific comorbidities, risk factors, microbiologic flora, and even geographical location may influence the causative infectious organism [2]. Although an unlikely pathogen, *Capnocytophaga* spp. are a part of normal oral flora in humans and animals that have been known to cause infections in certain circumstances. Herein, we present the case of a 62-year-old man with newly diagnosed chronic lymphocytic leukemia (CLL) complicated by a pleural empyema caused by *Capnocytophaga ochracea*.

Patient case

A 62-year-old Caucasian male presented to his primary care provider with complaints of weight loss, shortness of breath, and cough that had worsened over the previous three weeks. His past medical history was significant for gout, and his family history included leukemia in his brother. He had no significant travel history or exposure to pets, wild animals, or sick contacts. A chest radiograph (CXR) performed in the outpatient setting revealed a large left pleural effusion. He was then referred to our facility for further work-up.

On admission, the patient was afebrile and baseline laboratory values revealed a white blood cell (WBC) count greater than 220,000 cells/mm^3 with 91 % lymphocytes, hemoglobin 8.4 g/dL, platelets 171,000 cells/mm^3, serum creatinine 1.1 mg/dL, lactate dehydrogenase (LDH) 121 units/L (range 140–271 units/L), ferritin 599 ng/dL (range 22–300 ng/dL), immunoglobulin G (IgG) 260 mg/dL (range 635–1,741 mg/dL), and a negative hepatitis panel. A computed tomography (CT) scan of the chest confirmed the presence of a large, loculated left pleural effusion with multiple septations, mediastinal, axillary, and retroperitoneal lymphadenopathy, as well as hepatomegaly and splenomegaly (Fig. 1). Peripheral blood flow cytometry and fluorescent in-situ hybridization (FISH) analysis were consistent with CLL.

On day 4 of hospitalization, an ultrasound guided thoracentesis was performed and removed 60 mL of straw-colored fluid. Pleural

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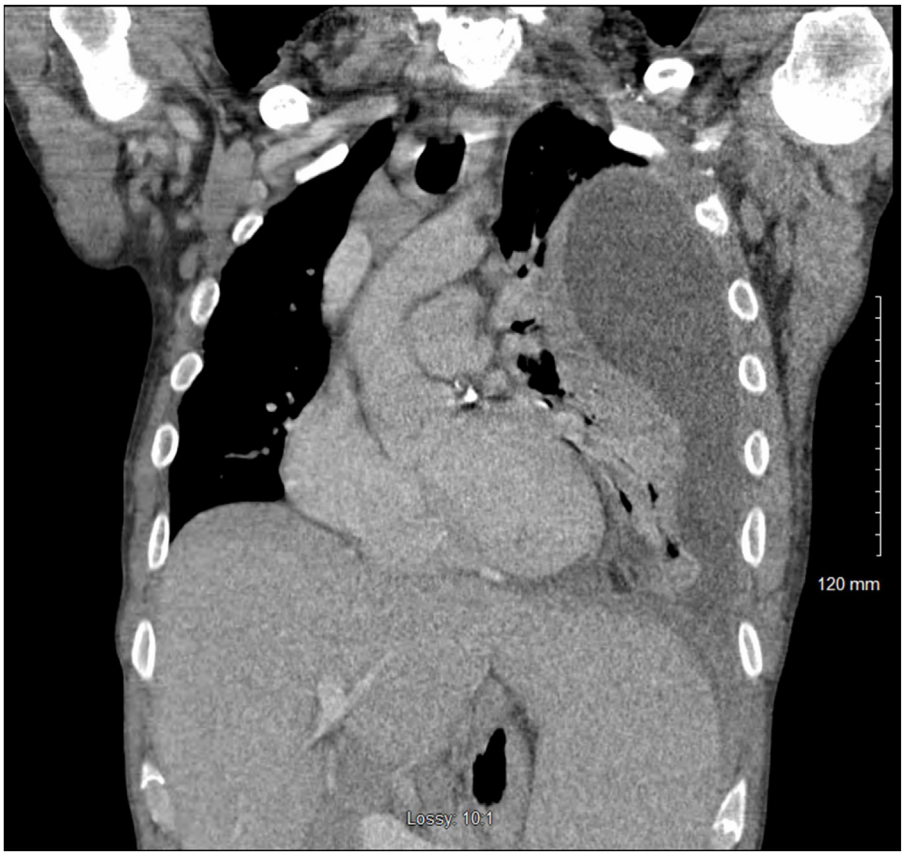

Fig. 1. Computed tomography (CT) scan chest coronal view demonstrated a large, loculated left pleural effusion (17.2 cm anteroposterior x11 cm transverse x25.1 cm craniocaudal) with multiple septations, compressive atelectasis adjacent to the left effusion with near complete collapse of the left lower lobe and partial collapse of the left upper lobe.

fluid analysis revealed pH 7.1, WBC 19,300 cells/mm^3 (neutrophils 68 %, monocytes 32 %), red blood cells (RBC) 63,406 cells/mm^3, glucose < 10 mg/dL, protein 4 g/dL, LDH 2928 units/L, consistent with an exudative effusion based on Light's criteria (pleural fluid protein/serum protein = 0.74, pleural fluid LDH/serum LDH = 24.2) [3], but Gram stain was negative and cytology was negative for malignant cells. On day 8 of hospitalization, video-assisted thoracoscopic surgery (VATS) was then performed with chest tube insertion which removed 400 mL of thick fluid indicative of an empyema Gram stain was negative, but flow cytometry of pleural tissue revealed minimal involvement by CLL. Anaerobic Gram negative bacilli were isolated after 72 h of incubation from both pleural fluid cultures, but had to be sent out for further identification. However, no antibacterial therapy was initiated postoperatively as this was believed to be a malignant pleural effusion.

The patient remained afebrile with a WBC > 70,000 cells/mm^3 throughout the entire admission but continued to improve to the point where chest tubes were removed on day 14 of hospitalization. On day 15 of hospitalization, the reference laboratory was able to identify these anaerobic Gram negative bacilli as two species of *Capnocytophaga ochracea*, of which β-lactamase activity was detected in only one isolate. The infectious diseases (ID) team was then consulted to assist with further management of the patient. However, prior to their evaluation and initiation of antibacterial agents, the patient left against medical advice. It was recommended that an outpatient prescription for amoxicillin-clavulanate 875 mg-125 mg twice daily for 30 days be sent to the patient's pharmacy and that he follow-up in the outpatient ID clinic.

The patient failed to fill the prescription for amoxicillin-clavulanate and did not follow-up with outpatient ID. However, one month after discharge, he followed-up with hematology/oncology and was initiated on ibrutinib, a tyrosine kinase inhibitor, for his CLL. In addition, a repeat chest CT again revealed a large complex effusion/empyema in the left lung with new air-fluid levels (Fig. 2). He underwent left thoracentesis during which 550 mL of thick purulent fluid was drained. The Gram stain was negative, but the culture again revealed a β-lactamase producing *C. ochracea* after 5 days of incubation. Pleural fluid analysis revealed pH 6.6, WBC 199,054 cells/mm^3 (neutrophils 98 %, monocytes 2 %), RBC 73,108 cells/mm^3, glucose < 10 mg/dL, protein 4 g/dL, LDH > 12,000 units/L, and minimal involvement by CLL on flow cytometry. Additional attempts by the hematology/oncology and infectious diseases clinics to contact the patient were unsuccessful and he was lost to follow-up from both services.

Discussion

Capnocytophaga spp. are Gram negative bacilli with slender tapered ends that are capnophilic, facultative anaerobes [4]. *C. gingivalis, C. granulosa, C. haemolytica, C. leadbetteri, C. ochracea,* and *C. sputigena* are normal flora of the human oral cavity, while *C. canimorsus* and *C. cynodegmi* are found in the oral cavities of dogs and cats [5]. These organisms are not typically pathogenic in humans. Most bloodstream infections occur as a result of animal bites, closed-fist facial injuries, and immunosuppression or malignancy, which is most frequently observed in those with neutropenia (absolute neutrophil count [ANC] < 500

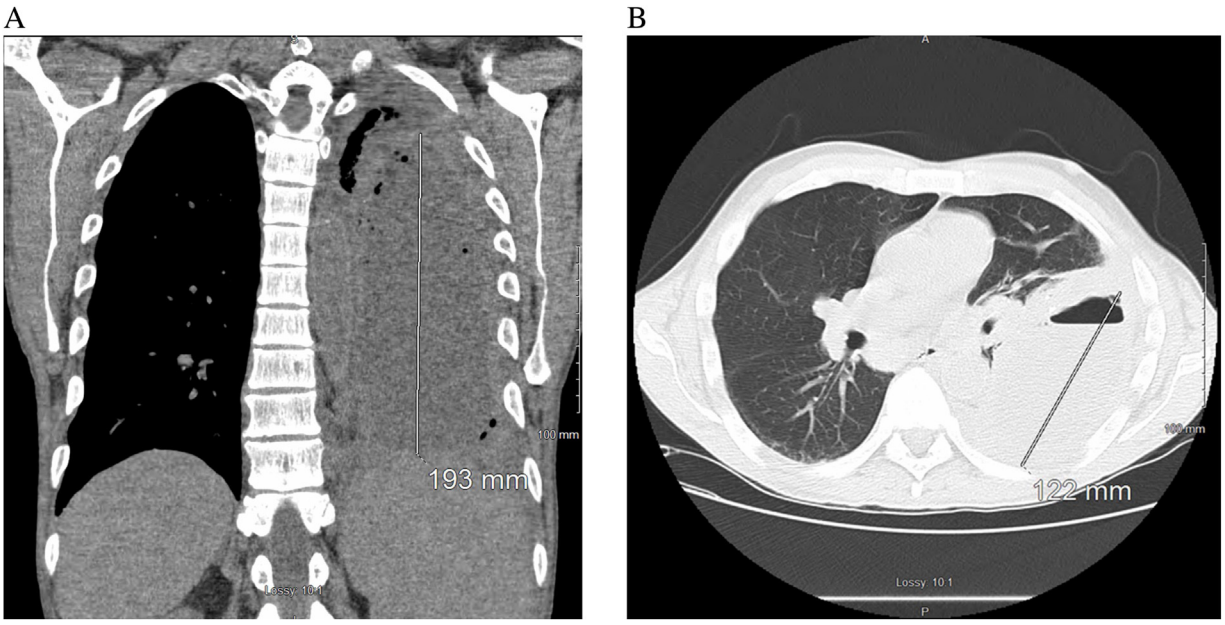

Fig. 2. Computed tomography (CT) scan chest coronal (A) and axial (B) views again demonstrated large complex effusion/empyema in the left lung (12 cm anteroposterior x 7 cm transverse x 19.3 cm craniocaudal) with multiple air foci within the collection.

cells/mm^3) [6]. Periodontitis may also occur in those with poor oral hygiene.

Underlying comorbidities and risk factors frequently predict the infectious etiology in pleural effusions and empyemas [2]. In patients with a history of pulmonary infections, *Streptococcus* spp. and anaerobes are the most common organisms identified, while *S. aureus*, Enterobacteriaceae, and *Enterococcus* spp. occur in fewer cases [1,12]. Anaerobes are associated with aspiration and poor oral hygiene, while patients with diabetes mellitus are more likely to have empyemas caused by *Klebsiella pneumoniae*. Patients that have undergone thoracic surgery or pneumonectomy have a higher likelihood of having an empyema caused by MRSA, Enterobacteriaceae, *Pseudomonas* spp., or fungi. *S. aureus* and fungi are the most common etiologies in immunodeficient patients. Alternatively, *Capnocytophaga* spp. pleural effusions and empyemas are uncommon with only a few cases being previously reported (Table 1) [7–11]. A case of pleural empyema caused by *Capnocytophaga* spp. following a laparoscopic Nissen fundoplication was previously described but has not been included in this table due to lack of specific details [11]. These cases reveal the diversity of patients with pleural infections due to *Capnocytophaga* spp. While other infectious etiologies are associated with specific clinical factors, a common risk factor for *Capnocytophaga* spp. pleural effusions and empyemas remains unknown. The limited number of reported cases may be related to difficulties isolating these organisms and the low occurrence of endogenous infections caused by *Capnocytophaga* spp. Many strains of *Capnocytophaga* spp. produce β-lactamases but are typically susceptible *in vitro* to β-lactam/β-lactamase inhibitor combinations, imipenem, tetracyclines, and chloramphenicol. Erythromycin, fluoroquinolones, and metronidazole have demonstrated inconsistent *in vitro* efficacy in these infections [4].

Although he had never received immunosuppressive chemotherapy, CLL is inherently immunosuppressive due to decreased function of the complement system and defective natural killer cells [13,14]. The complement system aids in modulating the immune system and preventing infection [15]. C1 and C4 levels, both of which are important components of the classical complement pathway, were found to be significantly reduced in patients with CLL compared to non-CLL patients in one study [16]. In addition, hypogammaglobulinemia is common in CLL, as observed in our patient [13]. While our patient did not have a history of poor oral hygiene, which is the most common source for *C. ochracea*, CLL may lead to mucosal immune defects [5,17]. As a result, patients with CLL are at increased risk of bacterial respiratory tract infections.

The interaction between *Capnocytophaga* spp. and the host immune response is quite complex. Infection with *C. canimorsus* compared to other Gram-negative bacteria results in a blunted inflammatory response, allowing it to evade the host immune system [18]. In particular, C1q-depleted serum has significantly less bactericidal activity against *C. canimorsus* and *C. cynodegmi* when compared to whole blood and serum [14]. Furthermore, the ability of *C. canimorsus* to harvest N-acetylglucosamine from host glycoproteins, including human IgGs, may contribute to its pathogenesis [19,20]. Although most studies have examined the pathogenesis of *C. canimorsus*, previous data have suggested that *C. ochracea* degrade IgG and even produce an immunosuppressive factor [18]. Most likely, this patient's newly developed CLL combined with the aforementioned virulence factors allowed *C. ochracea* in his oral cavity to invade and infect the pleural space.

Immunosuppression associated with the primary disease plays an important role in diagnosing and managing infectious diseases in patients with CLL. The route of acquisition in our patient was likely multifactorial and included aspiration of *C. ochracea* constituting part of the human oral microbiome coupled with the immune defects, specifically those related to mucosal immune function, associated with untreated CLL. Symptom onset of pleural effusions and empyemas caused by *Capnocytophaga* spp. varies. Similar to the insidious presentation associated with common causes of pleural empyema [21], our patient presented with a prolonged duration of respiratory symptoms compared to previous cases of patients with pleural effusions and empyemas caused by *Capnocytophaga* spp. [8–10]. Additionally, *Capnocytophaga* spp. infections can result in serious complications, such as septicemia, caused by these normally harmless bacteria. Empiric treatment

Table 1
Previous reports of patients with pleural effusions and pleural empyema caused by *Capnocytophaga* spp.

Citation	Past medical history	Clinical presentation	Organism isolated	Treatment	Outcome
Chambers et al. [9]	Waldenstrom macroglobulinemia with multiple courses of chemotherapies in previous 6 months	Fevers, chest pain, shortness of breath, cough x 2 days	*C. canimorsus*	Intravenous erythromycin and ceftazidime for 19 days	Afebrile after first hospital day, no further pulmonary complications
Kirchmair et al. [10]	Cirrhosis	Sudden dyspnea	*Capnocytophaga* spp.	Surgical drainage, imipenem 500 mg three times per day (no duration listed)	Resolution of empyema after one week of treatment, no long-term infectious complications at 16 months
Li et al. [8]	Hypertensive intracranial hemorrhages, vascular dementia, left parotid pleomorphic adenoma, no contact with pets except pet hamsters	Fever, cough, dysphagia x 3 days for first admission Hypoxia at follow up for second admission	*C. sputigena*	Amoxicillin-clavulanate followed by meropenem, drainage of effusion *via* chest tube, discharged on 6 weeks of cloxacillin Readmitted 1 month later with worsening right sided empyema, empirically started on meropenem and vancomycin with chest drain inserted to drain empyema Antibiotics de-escalated to ciprofloxacin and amoxicillin and discharged on day 14 of therapy to complete 6 weeks of therapy	Seen one month later in clinic with no reported problems and completed a total of 6 weeks of antibiotics

with a β-lactam/β-lactamase inhibitor combination or carbapenem is necessary due to increasing rates of β-lactamase production among strains of *Capnocytophaga* spp. [4]. As methods for isolating *Capnocytophaga* spp. continue to improve, more cases may be reported to allow clinicians a better understanding of the pathogenesis, clinical manifestations, and response to treatment. While infections caused by common bacterial pathogens occur at a higher rate in these patients, it is critical to recognize the increased risk of endogenously acquired infections of mucosal origin, some of which may be caused by unusual pathogens found in the human oral cavity.

Conclusion

Pleural effusions and empyemas caused by *Capnocytophaga* spp. may be underdiagnosed due to difficulties isolating these organisms and the low incidence of endogenous infections caused by *Capnocytophaga* spp. Additionally, certain *Capnocytophaga* spp. produce virulence factors that allow them to escape or limit host immune response to infection. In patients with CLL or other immunosuppressive diseases, it is crucial to consider all possible etiologies and pathogens to better direct antimicrobial therapy and prevent recurrence.

Author contributions

SAB, GMS, and DBC wrote and edited the manuscript, designed manuscript figures, and provided patient care; AFHM. and CFP edited the manuscript and provided expert advice in medical management.

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Declaration of Competing Interest

The authors report no conflicts of interest.

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