Case report

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

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**A R T I C L E   I N F O**

Article history:
Received 27 November 2019
Accepted in revised form 16 March 2020

Keywords:
*Capnocytophaga*
Pleural effusion
Empyema
Chronic lymphocytic leukemia

**A B S T R A C T**

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.

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**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 effusions...
fluid analysis revealed pH 7.1, WBC 19,300 cells/mm³ (neutrophils 68 %, monocytes 32 %), red blood cells (RBC) 63,406 cells/mm³, 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/mm³ 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 Capnoctytophaga 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/mm³ (neutrophils 98 %, monocytes 2 %), RBC 73,108 cells/mm³, 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

Capnoctytophaga spp. are Gram negative bacilli with slender tapered ends that are cappnophilic, facultative anaerobes [4]. C. gingivalis, C. granulosa, C. haemolytica, C. leadbetteri, C. ochracea, and C. spuitigena 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. 1. Computed tomography (CT) scan chest coronal view demonstrated a large, loculated left pleural effusion (17.2 cm anteroposterior x 11 cm transverse x 25.1 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.
cases the following and common the empyemas topohaga function cells likelihood described lactamase mon lactamases have only inhibitor remains important system of pneumoniae are caused by MRSA, Enterobacteriaceae, and Enterococcus spp., occur in fewer cases. 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). 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. 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.

Although he had never received immunosuppressive chemotherapy, CLL is inherently immunosuppressive due to decreased function of the complement system and defective natural killer cells. The complement system aids in modulating the immune system and preventing infection. 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. In addition, hypogammaglobulinemia is common in CLL, as observed in our patient. 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. 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. In particular, C1q-depleted serum has significantly less bactericidal activity against C. canimorsus and C. cynodegmi when compared to whole blood and serum. Furthermore, the ability of C. canimorsus to harvest N-acetylglucosamine from host glycoproteins, including human IgGs, may contribute to its pathogenesis. 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. 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, 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.
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 endogenous 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.

**Funding**

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

**Declaration of Competing Interest**

The authors report no conflicts of interest.

**Acknowledgements**

None.

**References**

[1] Feller-Kopman D, Light R. Pleural disease. N Engl J Med 2018;378(8):740–51.
[2] Maskell NA, Batt S, Hedley EL, Davies CW, Gillespie SH, Davies RJ. The bacteriology of pleural infection by genetic and standard methods and its mortality significance. Am J Respir Crit Care Med 2006;174(7):817–23.
[3] Light RW, Macgregor ML, Luchinger PC, Ball Jr. WC. Pleural effusions: the diagnostic separation of transudates and exudates. Ann Intern Med 1972;77(4):507–13.
[4] Jolivet-Gueguen A, Sioux JL, Tamani-Shacoori Z, Bonnasse-Mallet M. Antimicrobial treatment of Capnocytophaga infections. Int J Antimicrob Agents 2007;20(4):367–73.
[5] Zangeneh S, Bergman P. Whole genome sequencing identifies a novel species of the genus Capnocytophaga isolated from dog and cat bite wounds in humans. Sci Rep 2016;6:22919.
[6] Bennett JE, Dolin R, Blaser MJ, Mandell, Douglas, and Bennett's principles and practice of infectious diseases, eighth edition Philadelphia, PA: Elsevier/ Saunders; 2015 [2015].
[7] Bonatti H, Rosborth DW, Nachbaur D, Fille M, Aspock C, Hend L, et al. A series of infections due to *Capnocytophaga* spp in immunosuppressed and immunocompetent patients. Clin Microbiol Infect 2003;9(5):380–7.
[8] Li A, Tantibhay F, Chan D, Leong KK. *Capnocytophaga sp* as empyema. J Clin Microbiol 2013;51(1):272–4.
[9] Chambers GW, Westblom TU. Pleural infection caused by *Capnocytophaga canimorsus* formerly CDC group D2. Clin Infect Dis 1992;15(2):325–6.
[10] Kirkmaier R, Allerberger F, Bangler I, Egger C, Nachbaur K, Patsch JR, et al. Spontaneous bacterial pleural empyema in liver cirrhosis. Dig Dis Sci 1998;43(5):1129–32.
[11] Hourmont K, Klingler PJ, Wetscher G, Kafka R, Gadenstatter M, Bonatti H. *Capnocytophaga canimorsus* pleural empyema following laparoscopic Nissen fundoplication. A rare complication, a rare pathogen. Surg Endosc 2000;14(9):866.
[12] Reichert M, Hecker M, Witte B, Bodner J, Padberg W, Weigand MA, et al. Stage-directed therapy of pleural empyema. Langenbecks Arch Surg 2017;402(1):15–26.
[13] Hilal T, Gea-Banacloche JC, Leis JF. Chronic lymphocytic leukemia and infection risk in the era of targeted therapies: linking mechanisms with infections. Blood Rev 2018;32(5):387–99.
[14] Zangeneh S, Bergman P. Rapid killing of *Capnocytophaga canimorsus* and *Capnocytophaga cynodegmi* by human whole blood and serum is mediated via the complement system. Springerplus 2015;4:517.
[15] Vignesh P, Rawat A, Sharma M, Singh S. Complement in autoimmune diseases. Clin Chim Acta 2017;465:123–30.
[16] Fust G, Czink E, Minh D, Mizlaz Z, Varga I, Hollan SR. Depressed classical complement pathway activities in chronic lymphocytic leukaemia. Clin Exp Immunol 1985;60(3):489–95.
[17] Tsiodras S, Saromis G, Keating MJ, Kontoyiannis DP. Infection and immunity in chronic lymphocytic leukemia. Mayo Clin Proc 2000;75(10):1039–54.
[18] Shin H, Mally M, Kuhn M, Paroz C, Cornelis GR. Escape from immune surveillance by *Capnocytophaga canimorsus*. J Infect Dis 2007;195(3):375–80.
[19] Renzi F, Manfredi P, Mally M, Moés S, Jeno P, Cornelis GR. The N-glycan glycoprotein deglycosylation complex (Gpd) from *Capnocytophaga canimorsus* deglycosylates human IgG. PLoS Pathog 2011;7(6):e1002118.
[20] Renzi F, Manfredi P, Dol M, Fu J, Vincent S, Cornelis GR. Glycan-foraging systems reveal the adaptation of *Capnocytophaga canimorsus* to the dog mouth. MBio 2015;6(2):e02507.
[21] Bartlett JC. Anaerobic bacterial infections of the lung and pleural space. Clin Infect Dis 1993;16(Suppl. 4):S248–55.