



Case report

Capnocytophaga canimorsus sepsis in a methotrexate-treated patient with rheumatoid arthritis



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ABSTRACT

Capnocytophaga canimorsus is a gram-negative rod that can be transmitted primarily by dog bites. This life-threatening organism commonly causes sepsis in patients with splenectomy or alcoholism. A 53-year-old rheumatoid arthritis male treated with methotrexate (MTX) for 5 years was admitted for a 4-day history of fever and dyspnea. He had been bitten on a finger by the family dog 4 days before onset. Laboratory tests revealed pancytopenia, acute renal failure, and evidence of disseminated intravascular coagulation, and he subsequently developed acute respiratory distress syndrome. Furthermore, blood cultures grew gram-negative bacilli and despite intensive treatment, he died 5 days after admission. Later, *C. canimorsus* was identified from his culture samples using a species-specific polymerase chain reaction. *C. canimorsus* infections should be considered in the differential diagnosis of sepsis for immunocompromised hosts following animal bites.

Introduction

C. canimorsus is a fastidious, capnophilic gram-negative rod (GNR) that occurs primarily the oral flora of dogs [1,2]. In addition to sustaining an animal bite or exposure to saliva, the majority of severely infected patients are asplenic or suffer from alcoholism [1–3]. Despite the low incidence of *C. canimorsus* infections, the pathogen can cause life-threatening diseases such as sepsis, meningitis, and endocarditis [1–3]. *C. canimorsus* sepsis has a high mortality rate (19–36%) [1–5]. Suzuki et al. have found that, up until 2015, 14 of 55 patients infected with *C. canimorsus* in Japan died (unpublished data). The pathogen is difficult to culture due to its slow growth and specific requirements for nutrients. Moreover, it has the ability to escape the host's immune system [1]. Thus, the majority of cases with *C. canimorsus* infections are diagnosed late. We herein report a rare and fatal case associated with *C. canimorsus* sepsis in a rheumatoid arthritis (RA) patient treated with methotrexate (MTX).

Case report

A 53-year-old male visited a primary care physician after a 3-day history of fever and dyspnea. He had a 10-year history of RA that was well managed by oral MTX 10 mg/week and low-dose prednisolone (PSL) 2 mg/day for 5 years. The patient did not drink alcohol or smoke. He had been bitten on his left index finger by the family dog 4 days prior to symptom onset, but did not report the bite to his physician. Diagnosed as having a viral infection, he was discharged home.

Since symptoms worsened rapidly the next day, he was transferred to the emergency department of our hospital. At the time of admission, the patient was found to have a bite wound from the family dog with no signs of cellulitis or erythema (Fig. 1). Vital signs were as follows: blood pressure, 63/52 mmHg; heart rate, 129 beats/min; respiratory rate, 40/min; body temperature, 38.0 ° Celsius; and oxygen saturation, 100% at 3 L/min of oxygen. In addition, his laboratory results revealed pancytopenia (white blood cell count: 1300/μL; hemoglobin: 11.7 g/dL; platelet count: 6000/μL), a high-grade inflammatory status (CRP: 31.47 mg/dL; procalcitonin: 83.0 ng/mL), and renal impairment (creatinine: 4.97 mg/dL). Coagulation studies showed a prolonged

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Fig. 1. Index finger of the patient showing a wound from a dog bite without cellulitis and erythema.

prothrombin time-international normalized ratio of 1.4 and an increased fibrin/fibrinogen degradation products of 157.4 ng/mL. These findings were suggestive of septic shock and disseminated intravascular coagulation (DIC). Chest computer tomography (CT) revealed ground-glass opacity with consolidation in the subpleural regions of the bilateral lower lobes (Fig. 2A). Blood samples were collected for culture analysis.

Immediately after admission, our patient was transferred to the intensive care unit (ICU), given massive fluid replacement, and was administered a single dose of 1 g meropenem. Moreover, he required platelet transfusion and nafamostat mesilate (a serine protease inhibitor) to treat sepsis-related DIC. For sustained hypotension despite massive fluid resuscitation, noradrenaline followed by hydrocortisone was initiated. On the second day, the intensive treatments did not improve the hypotension, and his respiratory condition worsened. Repeat CT showed progression of consolidations in the bilateral middle and lower lobes (Fig. 2B) and with the development of acute respiratory distress syndrome (ARDS), he underwent mechanical ventilation. During this time, GNR were isolated from his blood cultures. Based on this clinical course, we suspected septic shock, DIC, and ARDS was caused by *C. canimorsus* infection. However, on the morning of the third day, he suddenly presented with pupillary dilation and no light reflex.

Head CT showed cerebral hemorrhage and herniation. He died in the ICU 5 days after admission.

A slow-growing GNR was subcultured for 48 h, grew well on sheep blood agar plates and was positive for catalase and oxidase. After his expiration, we found multiple rods within the cytoplasm of neutrophils, which was consistent with previous reports of *C. canimorsus* infection (Fig. 3) [6]. Subsequently, the pathogen was identified as *C. canimorsus* using a species-specific polymerase chain reaction (PCR) and nucleotide sequence-analysis targeting the 16S ribosomal RNA gene [7]. Based on these results, the patient was diagnosed as having severe sepsis caused by *C. canimorsus*. The results from the antibacterial susceptibility test revealed sensitivity to carbapenems, macrolides, and several β -lactam drugs including penicillin G.

Discussion

Previously, it was assumed that *C. canimorsus* infection morbidity is high in patients with a history of splenectomy or alcoholism; however, in recent retrospective analyses, approximately 40% of infected patients have been reported to be healthy individuals without such medical histories [1,2]. Our patient had neither undergone splenectomy nor had alcoholism but was receiving long-term oral administration of MTX for RA. *C. canimorsus* is found in the normal oral bacterial flora of dogs and cats, and infected patients generally have a history of contact with these animals [1–3]. Our patient also had close contact with a pet dog and had suffered a finger bite. Therefore, *C. canimorsus* infection was strongly suspected at the time of GNR isolation. However, although *C. canimorsus* sepsis was intensively treated after the initial examination, he died during hospitalization. In serious cases of *C. canimorsus* sepsis, organ dysfunction, such as coagulopathy and acute kidney injury, can frequently be detected during the initial examination [3]. In order to successfully treat patients, antimicrobial treatment should start during the early stages before organ dysfunction develops. In high-risk patients with *C. canimorsus* infection, such as the present case, preventive administration of antimicrobial agents should be considered following dog or cat bites [1–3,8].

C. canimorsus infection can lead to sepsis, meningitis, endocarditis, and gangrene. In particular, the onset of sepsis is common and leads to a poor prognosis [1–5]. In our case, cellulitis or erythema was not evident at the bite site during initial examination, but the site was certainly likely to be the source of the fatal bacteremia. *C. canimorsus* is characterized by several well-known features: it survives well in phagocytic cells, is complement-resistant, and can readily infect the bloodstream [9,10]. Furthermore, in an *in vitro* system, *C. canimorsus* induces the production of proinflammatory cytokines and nitric oxide from macrophages at a lower rate compared with other pathogens [11,12]. *C.*

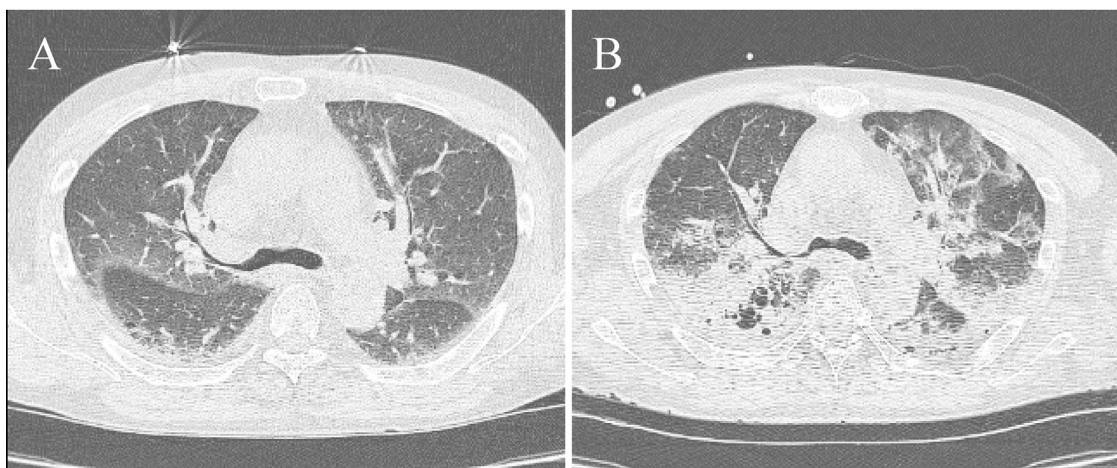


Fig. 2. Chest simple computed tomography at the time of admission (A) and after transfer to ICU (B).

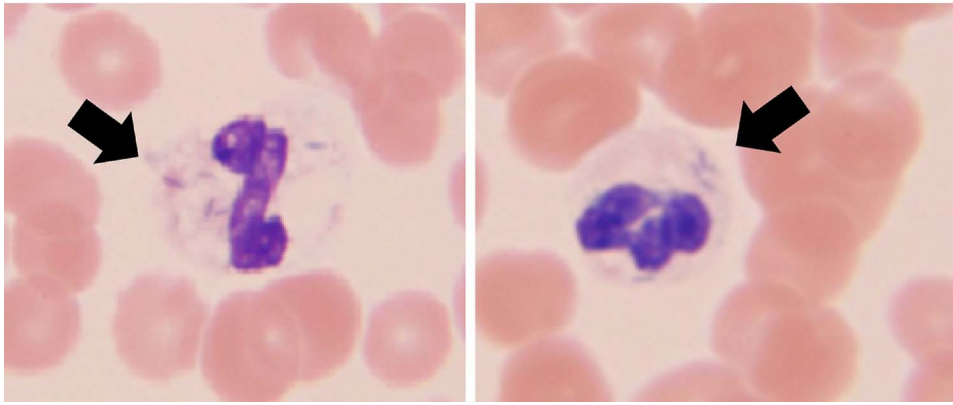


Fig. 3. Microscopic images of Giemsa staining of the peripheral blood smear from the patient, which show some slender rods in the cytoplasm of the neutrophils.

C. canimorsus infection readily leads to sepsis because of its ability to escape from the innate immunity of the host [2,9–12]. Cases associated with splenectomy or alcoholism are also frequently associated with impaired innate immunity, such as reduced macrophage function, which exacerbates *C. canimorsus* infections [1–4]. Although our patient had no history of splenectomy or alcoholism, the long-term oral administration of MTX most likely lowered the innate immunity against *C. canimorsus* infection. Some cases of *C. canimorsus* infections have been reported in immunocompromised hosts without a history of splenectomy or alcoholism [1,2]. In recent years, the number of patients with iatrogenic immunodeficiency including MTX-associated immunocompromised cases has increased. Careful attention should be given to the history of patients having close contacts with dogs and cats to prevent *C. canimorsus* infections.

C. canimorsus has a slow growth rate and requires a specific culture environment. To identify *C. canimorsus* using species-specific PCR and nucleotide sequence-analysis (targeting the 16S rRNA PCR gene), several days are required to allow for colonization to occur in blood cultures [13,14]. Therefore, an insufficient bacterial growth leads to negative blood cultures and, consequently, delayed diagnosis. In most cases with a severe clinical course, *C. canimorsus* infection is often identified only post mortem or during autopsy [4,15,16]. In patients with marked *C. canimorsus* sepsis, GNRs are often seemed in the stain of peripheral blood smears [1,2]. After he already died in the ICU, we could confirm slender rods in the cytoplasm of neutrophils on Giemsa stain of the peripheral blood smear (Fig. 3). Although a Gram-negative bacillus, it will stain blue on Wright-Giemsa staining. The diagnosis of *C. canimorsus* infections is often difficult, but it may be expedited by the recognition of this laboratory finding.

Matrix-assisted laser desorption ionization–time of flight (MALDI-TOF) mass spectrometry (MS) has been routinely used for the identification of bacteria and fungi from agar culture in some centers in Japan. Some reports have recently described that *C. canimorsus* was identified early and directly from positive blood cultures by using MALDI-TOF MS [17,18]. Moreover, a recent study has reported the analyses of circulating cell-free DNA derived from pathogens in plasma samples from septic patients by next-generation sequencing (NGS) [19]. Using this novel technique, a definitive diagnosis of *C. canimorsus* was possible even in the early stages before positive blood cultures [14]. In the near future, in many centers, we expect MALDI-TOF MS and NGS to be used for cases with sepsis caused by a variety of pathogens, including *C. canimorsus*, because a definitive diagnosis can be made earlier than by blood cultures [17–19].

Conclusion

Our case was a rare situation where the subject presented with MTX-associated immunodeficiency in which life-saving procedures were unsuccessful due to septic shock, DIC, and ARDS caused by *C.*

canimorsus infection. This infection has a low incidence (0.5 to 4.1 cases per million people) but with high mortality [1–4,20]. When the clinical course becomes severe following bites or scratches from dogs or cats, sepsis from *C. canimorsus* infection should be considered. In high-risk cases, such as those with a history of splenectomy, alcoholism, or iatrogenic immunodeficiency, early intervention is necessary.

Conflicts of interest

The authors declare no conflict of interest.

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