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Case Report

Fulminant septic shock caused by *Capnocytophaga canimorsus* in Italy: Case report

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ABSTRACT

Capnocytophaga canimorsus infection was recently recognized as a zoonosis. We report the first case of fulminant septic shock in Italy caused by this pathogen. The patient, with a history of splenectomy, died at the main hospital in Brescia with a presumptive diagnosis of sepsis. PCR and sequencing on post mortem samples confirmed *C. canimorsus* as a causative organism. Our purpose is to alert medical professionals to the virulence of *C. canimorsus* in asplenic and immunocompromised patients.

Introduction

Capnocytophaga canimorsus is a commensal microorganism present in the oral cavity of different animals, including dogs and cats. It can be transmitted to humans by pets' bites, scratches and licks. In immune competent individuals infections are usually asymptomatic, whereas patients with immune suppression and/or asplenia are at high risk of severe infections such as sepsis, meningitis, endocarditis and pneumonia (Butler, 2015). Fatal septic shock caused by *C. canimorsus* infection has only been rarely reported (Zazula et al., 2015). Here we describe, for the first time in Italy, a case of *C. canimorsus*-related fulminant septic shock.

Case report

In November 2017, at 2 p.m., a 22-year-old man with a history of spherocytosis and splenectomy (at the age of 11) was admitted at the Emergency Department of the main hospital in Brescia. On admission, he declared that the first symptoms occurred earlier than 20–24 h. He was awake and oriented, and presented with headache, vomiting, muscle pain, fever (39 °C) and facial petechiae appeared 3–4 h before admission and rapidly spreading to the trunk and limbs. A septic shock was suspected. His condition rapidly worsened, requiring urgent hospital admission. At 2:40 p.m., upon arrival to the Intensive Care Unit (ICU), he had severe arterial hypotension with absent peripheral pulse, heart rate of 150/min, and marked tachypnea (respiratory rate of 30–35 breaths/min). Arterial blood gas analysis revealed severe metabolic acidosis with hyperlactatemia (pH 7.1; lactates 10.5 mmol/L). After invasive monitoring position, the first blood pressure was 60/40. Laboratory tests on blood showed the following results: acute-phase protein C: 127 mg/L, creatinine: 3.58 mg/dl, total bilirubin: 3.33 mg/dl, alanine aminotransferase: 97 U/L, leukocytosis: (15.620/ml). Moreover, blood analysis showed hemoconcentration, with hemoglobin concentration of 20.1 g/dl, and coagulopathy with unmeasurable PT and PTT due to undetectable fibrinogen and severe thrombocytopenia (18.000/ml). In the ICU, the provisional diagnosis was septic shock of unknown cause. The patient was anuric and severely hypoxic with undetectable oxygen saturation at pulse oximetry despite aggressive intravenous fluid

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resuscitation and oxygen therapy. At clinical examination, there was intense peripheral vasoconstriction, marked cyanosis of the extremities and confluent petechiae all over the body.

According to clinical presentation meningococcal sepsis diagnosis was supposed, blood was drawn for blood culture and PCR diagnosis of the potential pathogens, and treatment with ceftriaxone (3 g) was initiated. Severe hypotension persisted despite high-dose, continuous i.v. infusion of noradrenaline and bicarbonate followed by adrenaline, terlipressin, and hydrocortisone. Despite emergent tracheal intubation and mechanical ventilation with 100% oxygen, the patient developed plasma extravasation with massive pulmonary edema and edema of the trunk and extremities. Bradycardia ensued rapidly followed by cardiac arrest refractory to cardiopulmonary resuscitation. At 5 p. m. the patient was declared dead.

A Gram stain of blood was negative, as well as serum-soluble antigens for *Neisseria meningitides* (group A,B,C,Y and W135), *Haemophilus influenza, Streptococcus pneumoniae, Streptococcus agalactiae, Listeria monocytogenes,* and *Escherichia coli* K1. PCR analysis excluded the presence of *Neisseria meningitidis*, *Haemophilus influenzae* or *Streptococcus pneumoniae* in the blood sample. Blood cultures under aerobic and anaerobic condition showed no growth of bacteria.

Post-mortem examination revealed cutaneous purpura with diffuse petechiae, bilateral pleural and pericardial effusion, massive lung edema, gastrointestinal hemorrhage involving the stomach and duodenum and massive bilateral adrenal hemorrhagic necrosis. On histology, skin lesions showed intraluminal fibrin deposits corresponding to intravascular coagulation (Figure 1A); similar findings were observed in several other tissues. The bone marrow showed numerous macrophages containing red blood and nucleated cells in their cytoplasm, indicating hemophagocytosis (Figure 1B). Similar, albeit less pronounced, features occurred in Kupffer cells and lung macrophages. Numerous granulocytes were found in the liver sinusoids and lung interstitium, suggestive for a septic status; overt abscesses were undetectable. No pathogens were identified on Gram stain. Meninges were normal. Anatomical diagnosis revealed hemophagocytosis, disseminated intravascular coagulation, bilateral adrenal hemorrhagic necrosis and gastrointestinal hemorrhage.

Conventional blood culture broth of post-mortem intracardiac blood, pleural liquid and cerebral ventricular fluid samples were negative. The suspected infectious etiology of the shock was confirmed by the detection of the pathogen in all post-mortem-collected fluids by sequencing of the 16S ribosomal RNA genes and identifying *C. canimorsus* (628-bp amplification product with 100% identity with strain CcD131 on Basic Local Alignment Search Tool) (Bémer et al., 2014). The same samples were subjected to PCR and sequencing by using *C. canimorsus* specific primers (Suzuki et al., 2010). Data obtained confirmed the presence of *C. canimorsus* in all tested samples (100% identity with the strain CcD131).

The patient did not show any sign of animal scratches or bites. However, since the patient owned a dog as pet, pharyngeal swabs and saliva samples were collected from the animal and subjected to molecular analysis. PCR and sequencing confirmed the presence of *C. canimorsus* in all tested dog samples.

Discussion

C. canimorsus is a commensal rod shaped Gram negative bacterium hosted in the oral cavity of different domestic pets. The microorganism is transmitted to humans by animal bites, scratches and licks. In case of occurrence of risk factors, such as asplenia, long history of alcohol abuse, cirrhosis, immunosuppressive therapy, the infection may have serious consequences. The most common presentation in risky patients is sepsis, meningitis, osteomyelitis, peritonitis, endocarditis, pneumonia or septic arthritis (Gaastra and Lipman, 2010; Griego et al., 1995). All over the world, 81 cases of fatal *C. canimorsus* infection over 484 total documented cases have been reported from 1961 to 2014, with a higher incidence in USA, The Netherlands, Denmark and France (Butler, 2015). *C. canimorsus* is one of the most lethal of sepsis pathogens ever described, with its estimated-fatality rate of about 26% (Butler, 2015). Patients with asplenia are more prone to overwhelming infection due to encapsulated organisms which can progress rapidly and can be fatal (Dudley et al., 2006). This implicates that spleen is a key organ for protection against *C. canimorsus* infection. Splenic macrophages in the red pulp are important cells of the innate immune system for removing bacteria from the blood. In *C. canimorsus* sepsis, which can develop as fast as one day after a dog bite, it is clearly the early phagocytosis of the innate immune system that has failed because specific antibody requires a longer time to develop. For patients with spleen, splenic function may be depressed by immunosuppressive therapies, irradiation, alcoholism or other diseases (Oehler et al., 2009). The recognition of *C. canimorsus* as the cause of severe infections after pet exposure depends on improved laboratory methods for the identification of this fastidious bacterium in clinical samples. Our case is the first Italian clinical report of a fulminant fatal sepsis caused by *C. canimorsus.* Only a few invasive *C. canimorsus* infections have been reported in Italy up to date. It is worth noting that these occurred in apparently immunocompetent patients who recovered from endocarditis (Frigiola et al., 2003), brain abscess (Ulivieri et al., 2008), septic shock and meningitis (Bertin et al., 2018).

Capnocytophaga species are regarded as difficult to culture because of their specific requirements for nutrients and long-term incubation to observe growth and colony formation. Often, the microorganism cannot be detected by standard laboratory

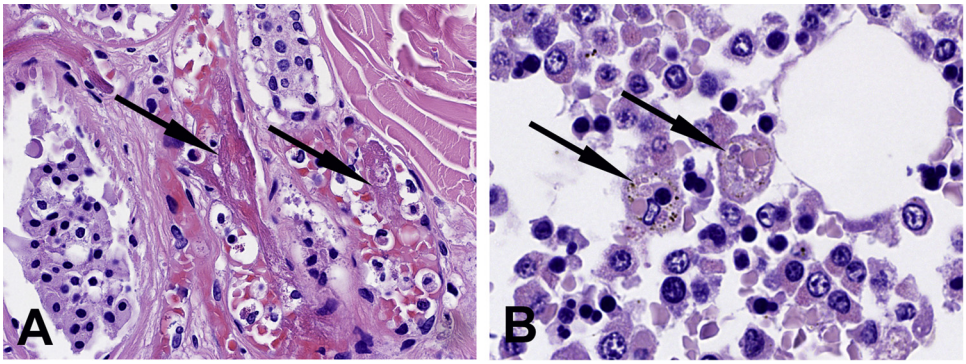

Figure 1. (A) Skin biopsy showing intravascular fibrin deposits (arrows), with partial occlusion of the lumen (Haematoxylin/Eosin). (B) Bone marrow shows macrophages with intracytoplasmic red cells and nucleated cells (arrows), (Haematoxylin/Eosin).

methods. Our diagnosis has been based on an accurate molecular method of bacteria identification. We first obtained a pure PCR product using universal 16S rRNA primers that was sequenced and aligned against bacterial DNA database. Then we confirmed the presence of *C. canimorsus* in clinical samples by using a species-specific set of primers. *C. canimorsus* is an unexpected bacterium and to a certain extent, unknown in ICU and in the diagnostic laboratory practice. PCR diagnostics provided clear and robust evidence of the causative organism, which would not be identified by using standard laboratory methods. Therefore, we believe it represents a useful and rapid tool for pathogen detection in selected cases of sepsis of unknown etiology.

Incidence of *C. canimorsus* infection is expected to increase over time because of a rising incidence of splenectomy due to injuries and accidents, or to impaired immune responses due to a high prevalence of alcoholism, immunosuppressive therapies, aging of human population, together with popularity of pet ownership due to a public perception of their safety. In particular, preventive strategies in reducing post-splenectomy infections include education, immunoprophylaxis and chemoprophylaxis. The potential seriousness of post-splenectomy sepsis and rapid time course of progression should be explained to patients who also have to be instructed to seek immediate medical attention in the event of any acute febrile illness. Further, patients should be educated about the risk of *C. canimorsus* through animal contact.

Research has recently demonstrated that animal-assisted therapy can yield many positive outcomes for hospitalized patients' well-being (Lundqvist et al., 2017). Animal therapy is becoming more and more popular, with hospitals letting pets visiting their sick owners. *C. canimorsus* infection is an extremely rare event. However, this possibility should be considered with caution whenever severely compromised immunity is suspected.

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Conflict of interest

The authors declare that they have no competing interests.

Ethical approval

The authors declare that the ethical approval was not required for this study

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