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CASE REPORT

Septic shock caused by Capnocytophaga canimorsus in a patient with heterozygous Pelger-Huët anomaly

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Abstract

Capnocytophaga canimorsus is a Gram-negative bacillus of the commensal flora of dogs and cats that can cause infections in humans through bites, scratches or contact with oral secretions. It can be difficult to identify in clinical microbiology laboratories because of the need for specific culture media. We present the case of a patient with no relevant medical history who was admitted with septic shock, where blood smear examination was crucial for the etiologic diagnosis of *Capnocytophaga canimorsus* infection. The patient was also diagnosed Pelger-Huët anomaly, a condition causing a defect in neutrophil chemotaxis, which may have contributed to the severity of the infection.

Keywords Capnocytophaga canimorsus · Septic shock · Pelger-Hüet anomaly · Bites · Slow-growing bacteria · Immunosuppression

Case presentation

A 38-year-old woman with a medical history of hypothyroidism treated with hormone replacement therapy presented to the Emergency Department complaining of nausea, vomiting, abundant greenish diarrhea, and fever of up to 39 ºC for 12 h, subsequently associated with sudden abdominal pain. Conservative management was performed in the Emergency Department after blood tests revealed no remarkable findings and she was discharged home. She returned hours later for persistent symptoms associated with acute respiratory failure. She had a very distended abdomen with peritoneal signs and laboratory parameters were suggestive of sepsis (metabolic acidosis with pH 7.17, HCO3- 10 mmol/L, hyperlactacidemia 11 mmol/L, procalcitonin 47 ng/mL) and disseminated intravascular coagulation (22.000 platelets and undetectable fibrinogen). A CT scan showed signs of general hypoperfusion and pulmonary edema. She was admitted to the Intensive Care Unit, requiring orotracheal intubation, high-dose norepinephrine, broad-spectrum antibiotic treatment after extraction of microbiological cultures (meropenem and linezolid), and corticosteroids. Continuous venovenous hemodiafiltration was started. An exploratory laparotomy was performed by the General Surgery Department, which did not reveal a specific etiology for her condition.

Over the next few hours, the patient developed severe heart dysfunction that required initiation of inotropic therapy. At reexamination, an erythematous-violet lesion on the index finger of the right hand with two small clean lesions and no cellulitis or signs of necrosis were observed. We found out that the patient had been bitten by a dog a few days earlier and had been taking amoxicillin–clavulanic acid.

She began to improve on the second day, allowing for weaning of vasoactive drugs and decreased oxygen support. Microbiological cultures and serologies were negative, suggesting the presence of a slow-growing microorganism in conventional culture media, and, therefore, a sample was sent for a polymerase chain reaction (PCR) analysis.

Given the laboratory abnormalities observed, a peripheral blood smear was sent to the Hematology Department to rule out thrombotic microangiopathies. No schistocytes suggestive of thrombotic microangiopathy were seen, but the presence of morphological abnormalities in the neutrophil series (with hyposegmented nuclei, vacuolated cytoplasm,

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and fusiform elements in the cytoplasm) was evident. Based on the suspicion of infection, a Gram staining of one of the slides was performed, showing intracellular Gram-negative bacilli (Fig. 1). A peripheral blood smear prepared from the first EDTA-anticoagulated blood sample that had been collected in the Emergency Department (when the patient had not yet met septic shock criteria) showed fusiform elements distributed among the blood cells as well as neutrophils with a dysplastic appearance (Fig. 2). A bone marrow aspiration was performed and revealed a normocellular marrow with predominance of myeloid series at different stages of maturation, and many toxic degenerative changes (intense cytoplasmic vacuolization and nuclear changes—hyposegmentation) without significant signs of dysplasia in the other

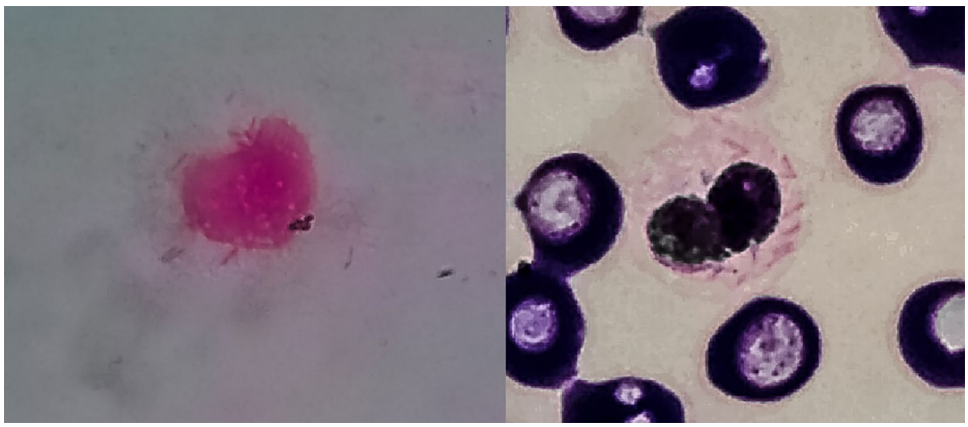


Fig. 1 Peripheral blood smear, Gram stain. Neutrophil with fusiform elements in the cytoplasm

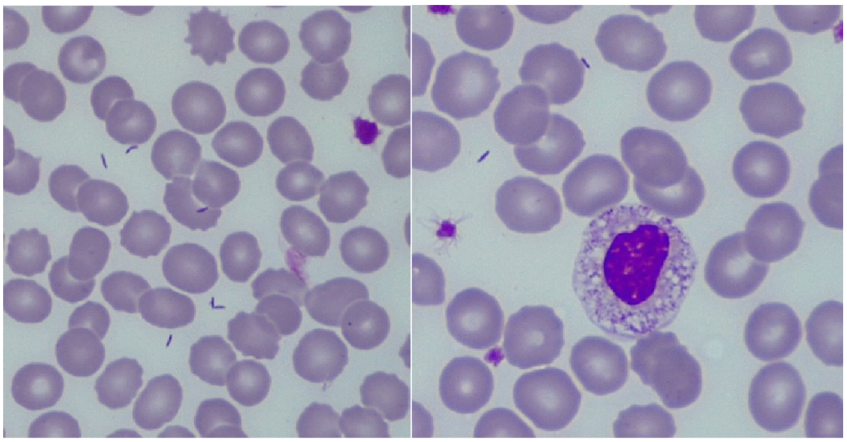
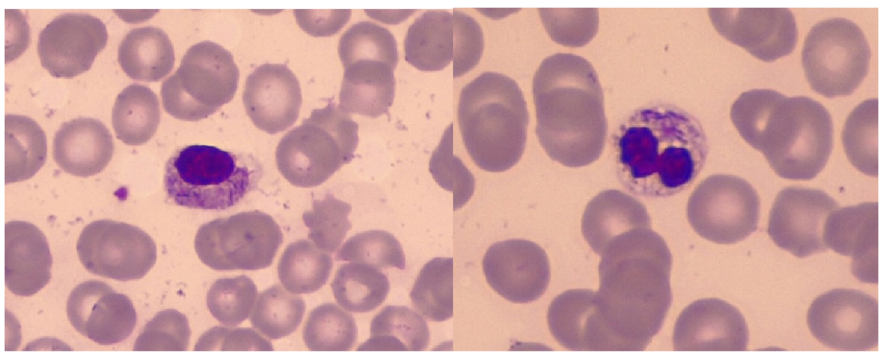


Fig. 2 **a** Peripheral blood smear. First sample. Fusiform elements distributed among the blood cells (left), as well as dysplastic-looking neutrophils (right) were observed (May-Grünwald-Giemsa × 1000). **b** Peripheral blood smear. Neutrophils with hyposegmented nuclei, vacuolated cytoplasm, and presence of fusiform elements in the cytoplasm (May-Grünwald-Giemsa × 1000)

a. Peripheral blood smear. First sample. Fusiform elements distributed among the blood cells (left), as well as dysplastic-looking neutrophils (right) were observed (May-Grünwald-Giemsa x1000).



b. Peripheral blood smear. Neutrophils with hyposegmented nuclei, vacuolated cytoplasm, and presence of fusiform elements in the cytoplasm (May-Grünwald-Giemsa x1000).

hematological cells. No cytogenetic abnormalities were observed. In addition, several bacilli were observed in one neutrophil.

On the sixth day, positive PCR results for *Capnocytophaga canimorsus* were obtained and antibiotic therapy was de-escalated. The patient evolved slowly but favorably and was transferred to the general ward after 1 month in the ICU. Her heart function recovered but not her renal function and she underwent a kidney transplant 2 years later.

After resolution of the acute condition, the cytoplasmic changes of neutrophils normalized, without vacuolization or presence of intracytoplasmic bacilli, but hyposegmented nucleus were still observed. Four months after diagnosis, these abnormalities persisted (Fig. 3), which led us to hypothesize that the patient could have a heterozygous Pelger-Huët anomaly.

Discussion

Animal bite infections are usually polymicrobial [3]. The genus *Capnocytophaga* (family *Flavobacteriaceae*) comprises slow-growing, fusiform or even pleomorphic Gram-negative bacteria. It consists of nine species [4, 5]. *Capnocytophaga canimorsus* is a Gram-negative bacillus that is part of the commensal flora of dogs and cats and can be present in human infections associated with animal bites, scratches or contact with oral secretions [6]. *C. canimorsus* is responsible for the vast majority of *Capnocytophaga* infections resulting from dog bites. It was first associated with severe sepsis in humans after dog bites in 1976 [1, 7]. Although the incidence of *C. canimorsus* infections is low (0.5–0.67 per million), it may be underestimated, because it can present as mild, flu-like symptoms and the bacteria is slow-growing [8].

Sepsis [9] and meningitis [10] are the most commonly described clinical forms, and the most common predisposing factors are immunosuppression from hyposplenia/asplenia (33%) and alcoholism (22%), although up to 40% of patients have no identifiable risk factors [2, 11]. Our patient had no known predisposing risk factors, but the cytological examination showed pseudo-Pelger-Huët abnormalities remained after the resolution of the acute condition. This raises the question of whether performing a cytological screening before screening for immunodeficiency disorders in patients with fulminant shock could be useful.

Pelger-Huët anomaly (PHA) is a benign trait with autosomal dominant inheritance characterized by hyposegmentation of the neutrophil's nucleus and excessive chromatin clumping. The morphologic abnormality in Pelger-Huët cells is known to be caused by a genetic defect in the lamina B-receptor (LBR) on chromosome 1q41-43, when the

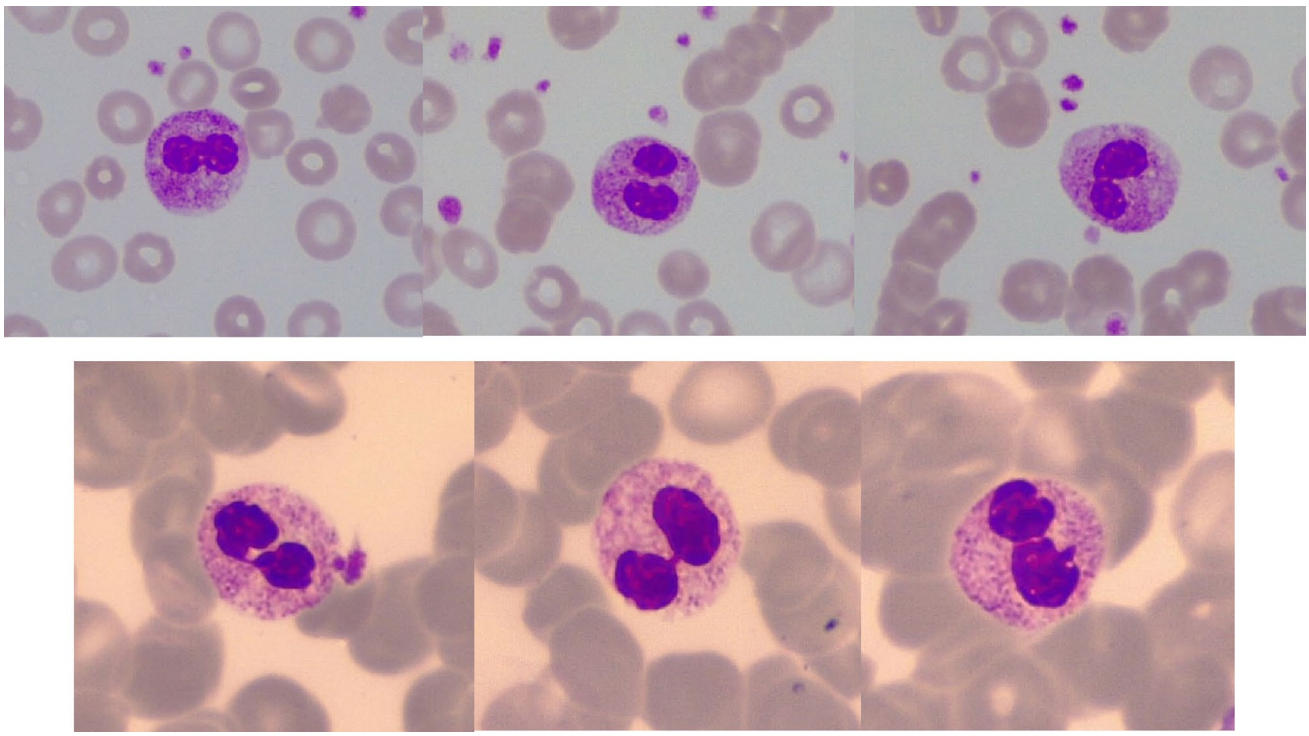


Fig. 3 Peripheral blood smear. **a** A few weeks after resolution of the acute condition, hyposegmented neutrophil without bacilli. (May-Grünwald-Giemsa × 1000). **b** Four months after diagnosis, hyposegmented neutrophils persist (May-Grünwald-Giemsa × 1000)

amount of LBR is half the normal amount, and the subject who was homozygous for the LBR mutation showed no nuclear segmentation (round or oval nuclei) [12]. In the heterozygous phenotypes, most of the neutrophils show a symmetrical bilobed nucleus with a "pince-nez" appearance. In severe infections, they can temporarily acquire a round nucleus as in the homozygous Pelger-Huët anomaly [13]. Bilobed neutrophils are also seen in acquired conditions (leukemoid reactions during severe bacterial infections, some medications, myelodysplastic syndromes (MDS)) and are known as pseudo-PHA, which are transient and reversible when the cause is resolved or persist or progresses in neoplasms like MDS without treatment [14, 15]. The persistence of these abnormalities once the infection has resolved, and in the absence of findings suggestive of MDS, suggest that it could be a case of heterozygous PHA. It has been suggested that the presence of a chemotactic defect in these neutrophils due to the lack of segmentation could impair their passage through the capillary pores [16] but no difference between normal neutrophils and PHA cells with regard to chemotaxis or microbiocidal activity have been found. The only functional defect identified has been an association between PHA and soft tissue infections, due to defective diapedesis. [17, 18] but their clinical implications remains to be elucidated.

Although cases of *Capnocytophaga canimorsus* infections have been published in Spain [19], this would be the first reported case in a patient with suspected heterozygous Pelger-Huët anomaly.

Identification of *Capnocytophaga canimorsus* in clinical microbiology laboratories can be difficult and is not always achieved as it requires enriched culture media (blood agar or chocolate agar) incubation with 5–10% CO2 or CHO3- to grow in both aerobic and anaerobic conditions. Cultures can take up to 14 days to become positive (average 6 days of incubation) or may not positivize in cerebrospinal fluid samples in conventional cultures, so rapid sequencing of the 16S rRNA gene represents a useful tool that improves targeted therapy [20]. Direct observation of bacteria in peripheral blood smears [20, 21] —an exceptional fact in most bacteremias—and appropriate clinical interview facilitate diagnosis.

As the incubation period is 1–8 days, our patient did not show significant symptoms during the first week after the bite. Initial symptoms were non-specific (general discomfort, nausea, vomiting, diarrhea, and fever) and rapidly progressed to septic shock with multiorgan failure despite having received the correct antibiotic therapy [24]. *C. canimorsus* evades the immune system in the early stages of infection [23].

Mortality related to this bacterium is high, even in immunocompetent patients [24, 25]. Based on two epidemiological studies and a review of published cases, the mortality rate from *C. canimorsus* infections is around 13–31%. However, mortality has not been studied in patients treated in ICU even though 35% of patients in a Dutch study required ICU admission [1, 9, 27, 28].

Among the known *C. canimorsus* serovars (A–K), three are associated with most human infections caused by dog bites (A, B, and C). No association between serovars and disease severity, immune status, alcohol abuse, or smoking has been found. Only a few strains of *C. canimorsus* are virulent in humans, and few dogs carry these dangerous strains. In fact, the three most prevalent serovars detected in human infections (91.8%) (A–C) represent only 7.6% of *C. canimorsus* isolated in dogs [8]. The serovar was not determined in our case.

Prophylactic antibiotherapy after a dog bite is recommended in at-risk patients [27]. However, since a non-negligible percentage (up to 40%) of immunocompetent patients are infected, it should be evaluated whether prophylactic amoxicillin-clavulanic acid should always be administered for 5 days after exposure. In the case of our patient, although she had received antibiotic therapy prior to admission, she still developed septic shock. A delayed antibiotic therapy initiation after the bite, mechanisms of evasion of the host's immune system by the bacteria, and/or the presence of a heterozygous Pelger-Huët anomaly are all potential causes that may have contributed to the septic course. As the congenial form is inherited in an autosomal dominant fashion, evaluation of other first degree relatives may be very informative to support our hypothesis.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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