An Immunocompetent Case of *Capnocytophaga canimorsus* Infection Complicated by Secondary Thrombotic Microangiopathy and Disseminated Intravascular Coagulation

Naoki Tani¹, Keiji Nakamura¹, Kosuke Sumida¹, Michio Suzuki², Koichi Imaoka² and Nobuyuki Shimono³

Abstract:
A 62-year-old woman with no previous history developed a *Capnocytophaga canimorsus* infection followed by thrombotic microangiopathy (TMA) and disseminated intravascular coagulation (DIC). She was treated with antibiotics and plasma exchange (PE) and recovered. *C. canimorsus* sepsis sometimes causes not only DIC but also TMA. The mortality of TMA is extremely high, so we should not hesitate to perform PE when a patient shows TMA symptoms.

Key words: *Capnocytophaga canimorsus*, sepsis, disseminated intravascular coagulation, emerging infection, thrombotic microangiopathy

(Intern Med Advance Publication) (DOI: 10.2169/internalmedicine.3110-19)

Introduction

*Capnocytophaga* spp. is part of the normal oral flora of dogs, cats, and humans, and there are nine species. Most serious and fatal cases are due to *Capnocytophaga canimorsus*. *C. canimorsus* infection is rare considering the frequency of animal bites and scratches, but patients can develop severe sepsis, and the mortality rate is over 30% (1). Furthermore, *C. canimorsus* sepsis can develop into thrombotic microangiopathy (TMA), which requires advanced treatment, such as hemodialysis or plasma exchange (PE).

We herein report an immunocompetent case of *C. canimorsus* sepsis complicated with TMA. The patient recovered because of adequate antibiotic therapy and prompt performance of PE.

Case Report

A 62-year-old woman with no previous history consulted her previous doctor with a fever, stomachache, and diarrhea. She had been bitten by her own dog two days before. She developed a fever over 38°C and had low blood pressure. She was transferred to our hospital with suspicion of septic shock.

On admission, an assessment of her vital signs revealed mild consciousness disorder of Glasgow Coma Scale E3V5M6, blood pressure of 93/53 mmHg, heart rate of 90 beats per minute, respiratory rate of 20 breaths per minute, and oxygen saturation of 97% under room air. A physical examination revealed left flank pain and a bite scar in her left hand without signs of infection. There was no lymphadenopathy, and her respiratory and heart sounds were normal.

Her laboratory data during admission are shown in Table. On admission, the laboratory data showed signs of disseminated intravascular coagulation (DIC; platelet 29,000/μL, D-dimer 39.0 μg/mL, PT INR 1.46, fibrinogen 165 mg/dL), mild elevation of bilirubin (1.7 mg/dL), and elevation of procalcitonin (13.80 ng/mL). Chest X-ray showed pulmonary congestion and bilateral pleural effusion. Contrast-enhanced computed tomography (CT) revealed complete non-enhancement of the spleen, suggesting...
DIC and started antibiotic therapy with piperacillin/tazobactam (days 1-3: 4.5 g ×3, days 4-9: 2.25 g ×4), administered thrombomodulin alfa (days 2-5: 12,800 U), and performed platelet transfusion because of bleeding from her mouth (days 2 and 4: 10 U). On day 3, slim Gram-negative rods were isolated from blood culture. Considering her episode of dog bite, we suspected this organism to be Capnocytophaga sp. Despite treatment for DIC and improvement of her coagulation, schistocytes appeared, and haptoglobin (determined by a nephelometry test) was undetectable on day 5. We diagnosed her with TMA because of the presence of four of the five main signs: a fever, thrombocytopenia, schistocyte, and renal involvement (2).

We started PE to treat TMA immediately after the diagnosis. The platelet count recovered, and the symptoms of hemolytic anemia disappeared after PE. PE was performed six times in total. A disintegrin-like and metalloprotease with thrombospondin type 1 motifs 13 (ADAMTS13) activity was 77.2%, and the inhibitor (both determined by an enzyme-linked immunosorbent assay) was negative (both examined on day 5). A stool culture examined on admission with Thrombotic Microangiopathy.

| reference | year | age/sex | exposure | risk factor | ADAMTS13/inhibitor | antibiotics | treatment | outcome |
|-----------|------|---------|----------|-------------|---------------------|-------------|-----------|---------|
| 8         | 1991 | 72/Male | Cat scratch | NA | not measured | GM | Steroids | Survive |
| 9         | 1996 | 53/Female | Dog lick | heavy smoker | not measured | PCG | PE | Survive |
| 10        | 1999 | 50/Male | Dog bite | NA | not measured | AMPC/CVA | PE | Survive |
| 11        | 1999 | 47/Male | Owned dog | alcoholism | not measured | AMPC/CVA | PE | Survive |
| 12        | 2001 | 66/Male | Dog bite | NA | not measured | CXM | Plasmapheresis | HD | Survive |
| 13        | 2012 | 72/Male | Dog bite | none | not measured | PIPC/TAZ | PE | Survive |
| 1         | 2013 | 56/Male | Dog bite | splenectomy | not measured | VCM | Steroids | Survive |
| 6         | 2016 | 61/Male | Dog bite | none | 39%/ not measured | MEPM | PE | Survive |
| 7         | 2018 | 63/Male | Owned dog | alcoholism | less than 1%/ not measured | CTRX | Plasma infusion | Survive |
| our case  | 2018 | 62/Female | Dog bite | none | 77.2%/ negative | PIPC/TAZ | PE | Survive |

NA: not available, PIPC/TAZ: Piperacillin/tazobactam, IPM: Imipenem, MEPM: Meropenem, CLDM: Clindamycin, ABPC: Ampicillin, ABPC/SBT: Ampicillin–sulbactam, PCG: Benzylpenicillin, NTL: Netilmicin , VCM: Vancomycin, AMPC: Amoxicillin, AMPC/CVA: Amoxicillin/clavulanate, OFLX: Ofloxacin, CTRX: Ceftriaxon, CXM: Cefuroxime, MNZ: Metronidazole, GM: Gentamicin, MFIPC: Flucloxacillin, PC: Pencillin, PE: plasma exchange, CRRT: continuous renal replacement therapy, HD: hemodialysis, HF: hemofiltration, HDF: Hemodiafiltration

**Figure 1.** CT revealed hepatomegaly, non-enhancement of the spleen, and lower gastrointestinal tract edema.
for Enterohemorrhagic *Escherichia coli*, which produces Shiga toxin, was negative. The species was identified as *Capnocytophaga sp.* on day 11, and we switched the antibiotics from piperacillin/tazobactam to ampicillin and amoxicillin on day 21 according to the susceptibility results. Schistocytes disappeared on day 27. The pathogen was finally identified as *C. canimorsus* by a genetic examination (polymerase chain reaction of the 16S rRNA gene and gyrB-specific gene) at the National Institute of Infectious Diseases, Japan.

**Discussion**

*Capnocytophaga spp.*, which is characterized by facultatively anaerobic, thin and fusiform Gram-negative rods, is part of the normal oral flora of dogs, cats, and humans. This organism includes nine species (3), of which six exist naturally in the human mouth, while the other three exist in animals’ mouths and infect humans through bites or scratches. *C. canimorsus*, which inhabits the oral cavity of dogs and cats, has the highest virulence of the three species and causes not only DIC but also TMA.

First, we diagnosed our case as one of *C. canimorsus* sepsis complicated by DIC. DIC mimics TMA-like symptoms, making it sometimes difficult to determine whether symptoms can be attributed to DIC, TMA, or both. In our case, despite treatment for DIC, schistocytes suddenly appeared, and thrombocytopenia and hemolytic anemia worsened despite improvements in the DIC markers, such as PT-INR, ATIII, and FDP (Fig. 2). We therefore diagnosed the patient with DIC complicated with TMA on day 5.

TMA presents with typical symptoms, such as hemolytic anemia, the appearance of schistocytes, and organ dysfunction caused by thrombosis. In addition to hemolysis, haptoglobin is consumed to bind free hemoglobin. From a pathological perspective, these symptoms are triggered by endothelial and vessel wall damage, which is caused by arteriolar and capillary thrombosis (4). TMA includes thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS), atypical HUS (aHUS) caused by error of complement control factor, and secondary TMA after infection, collagen diseases, malignancy, etc. We initially suspected this to be a case of TTP, but we dismissed this notion because the ADAMTS13 activity was normal (77.2%) and the inhibitor was negative. Shiga-toxin, which would trigger HUS, wasn’t detected. To diagnose aHUS, we must rule out the possibility of secondary TMA first, so we ultimately diagnosed her with secondary TMA after infection (5).

We searched the PubMed, for English-language reports of cases of *C. canimorsus* infection complicated by TMA and identified 10 cases, summarized in Table (1, 6-13). The ADAMTS13 activity was measured in only two previous case reports (6, 7) and was normal, as in the present case. This phenomenon has been described in some pathogenic organisms, such as bacteria, angioinvasive fungi, viruses, and rickettsiae, that cause endothelial injury (14). The mechanisms of TMA in *Capnocytophaga* infection cases with normal ADAMTS13 activity are unclear; however, it is said that *C. canimorsus* infection presents with a strong inflammatory response, leading to microvascular injury of the endothelium (15), which may induce the TMA onset. The mechanisms underlying the low ADAMTS13 activity are also unclear, but two hypotheses have been proposed: 1) ex-
cessive activation or damage of the endothelium (7) or 2) activation of granulocyte elastase and other proteases in DIC patients with sepsis (16). Our patient differed from other cases in that TMA developed secondary to DIC, whereas all previous cases were complicated with TMA from the outset. Platelet transfusions to patients suspected of having TTP are supposed to be contraindicated due to the risk of precipitating further thrombotic events (17), so we cannot exclude the possibility that platelet transfusion might have triggered TMA in our case.

Among the 10 previous cases (Table), the patients’ age ranges from 47 to 72 years old, with a mean age of 59 years old. There were four immunocompromised patients, alcoholism and post-splenectomy. Besides a dog-bite history, three patients had only a history of dog-lick or kept a dog as a pet, and one patient had a cat-scratch history. Some Capnocytophaga strains are β-lactamase-producing (18), so we should administer a β-lactamase inhibitor (such as piperacillin/tazobactam) or a carbapenem (such as meropenem) until the sensitivity is revealed. In our case, we changed the antibiotics after confirming that this strain was susceptible to benzyl penicillin. In most cases, PE was performed to treat TMA.

Once TMA occurred, the mortality was extremely high (over 90%) without PE, although it decreased to 22% with PE (2, 19). We must therefore bear in mind the possibility of the emergence of TMA, not only DIC, especially in cases of C. canimorsus infection.

The authors state that they have no Conflict of Interest (COI).

References

1. Ma A, Goetz MB. Capnocytophaga canimorsus sepsis with associated thrombotic thrombocytopenic purpura. Am J Med Sci 345: 78-80, 2013.
2. Scully M, Goodship T. How I treat thrombotic thrombocytopenic purpura and atypical haemolytic uremic syndrome. Br J Haematol 164: 759-766, 2014.
3. Zangenah S, Abbasi N, Andersson AF, Bergman P. Whole genome sequencing identifies a novel species of the genus Capnocytophaga isolated from dog and cat bite wounds in humans. Sci Rep 6: 22919, 2016.
4. James NG, Carla MN. Syndromes of Thrombotic Microangiopathy. N Engl J Med 371: 654-666, 2014.
5. Kato H, Yoshida R, Nagaku M. Pathology of complement-coagulation-related atypical hemolytic uremic syndrome. Jpn J Nephrol 56: 1058-1066, 2014.
6. Maezawa S, Kudo D, Asanuma K, Takekoshi D, Egashira R, Kashimoto S. Severe sepsis caused by Capnocytophaga canimorsus complicated by thrombotic microangiopathy in an immuno-competent patient. Acute Med Surg 4: 97-100, 2017.
7. Nori ILS, Rob F, Silvie S, Quirijn DM. Secondary thrombotic microangiopathy with severely reduced ADAMTS13 activity in a patient with Capnocytophaga canimorsus sepsis: a case report. Transfusion 58: 2426-2429, 2018.
8. Scarlett JD, Williamson HG, Dasdon PJ, Fassett R, Peel MM. A syndrome resembling thrombotic thrombocytopenic purpura associated with Capnocytophaga canimorsus septicemia. Am J Med 90: 127-128, 1991.
9. Finn M, Dale B, Isles C. Beware of the dog! A syndrome resembling thrombotic thrombocytopenic purpura associated with Capnocytophaga canimorsus septicemia. Nephrol Dial Transplant 11: 1839-1840, 1996.
10. Tobé TJ, Franssen CF, Zijlsta JG, de Jong PE, Steegeman CA. Hemolytic uremic syndrome due to Capnocytophaga canimorsus bacteremia after a dog bite. Am J Kidney Dis 33: e5, 1999.
11. Kok RHI, Wolfhagen MJHM, Mooi BM, Offerman JG. A patient with thrombotic thrombocytopenic purpura caused by Capnocytophaga canimorsus septicemia. CMI 5: 297-298, 1999.
12. Mulder AH, Gerlag PG, Verhoef LH, van den Wall Bake AW. Hemolytic uremic syndrome after Capnocytophaga canimorsus (DF-2) septicemia. Clin Nephrol 55: 167-170, 2001.
13. Michal B, Peter B, Raymond K. Capnocytophaga canimorsus infection presenting with complete splenic infarction and thrombotic thrombocytopenic purpura: a case report. BMC Res Notes 5: 695, 2012.
14. Booth KK, Terrell DR, Vesely SK, George JN. Systemic infections mimicking thrombotic thrombocytopenic purpura. Am J Hematol 86: 743-751, 2011.
15. Shahani L, Khardori N. Overwhelming Capnocytophaga canimorsus infection in a patient with asplenia. BMJ Case Rep bcr 2013207268, 2014.
16. Ono T, Mimuro J, Madoiwa S, Soejima K, Kashiwakura Y, Ishiwata A, Takano K, Ohmori T, Sakata Y. Severe secondary deficiency of von Willebrand factor -cleaving protease (ADAMTS13) in patients with sepsis-induced disseminated intravascular coagulation: its correlation with development of renal failure. Blood 107: 528-534, 2006.
17. Scully M, Hunt NJ, Benjamin S, Liesner R, Rose P, Peyvandi F, Cheung B, Machin SJ. Guidelines on the diagnosis and management of thrombotic thrombocytopenic purpura and other thrombotic microangiopathies. BJH 158: 323-335, 2012.
18. Maury S, Leblanc T, Rousselet P, Legrand P, Arlet G, Cordonnier C. Bacteremia due to Capnocytophaga species in patients with neutropenia: high frequency of β-lactamase-producing strains. Clin Infect Dis 28: 1172-1174, 1999.
19. George JN, Vesely SK, Terrell DR. The Oklahoma thrombotic thrombocytopenic Purpura-Hemolytic uremic syndrome (TTP-HUS) registry: a community perspective of patients with clinically diagnosed TTP-HUS. Semin Hematol 41: 60-67, 2004.