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【 CASE REPORT 】

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

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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

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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℃ 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 Fig. 1. On admission, the laboratory data showed signs of disseminated intravascular coagulation [DIC; platelet 29,000/μL, D-dimer 39.0 μg/mL, prothrombin time-international normalized ratio (PT-INR) 1.46, fibrinogen 165 mg/dL], mild elevation of bilirubin (1.7 mg/dL) and LDH (396 IU/L), and elevation of procalcitonin (13.80 ng/mL). Chest X-ray showed pulmonary congestion and bilateral pleural effusion.

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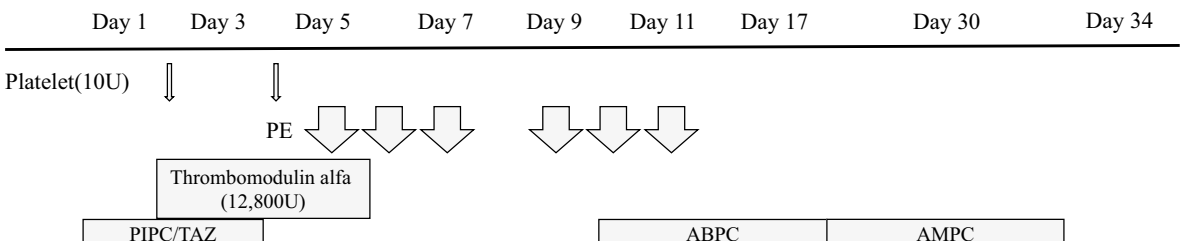

WBC (/μL)	4,300	7,800	7,800	15,500	22,100	16,700	7,100	9,700	8,100
Hb (g/dL)	**13.6**	**12.1**	**8.4**	**7.2**	**5.9**	**7.0**	**7.7**	**8.4**	**9.1**
Plt (*10^4/μL)	**2.9**	**1.7**	**1.6**	**1.4**	**4.1**	**19.7**	**58.1**	**44.3**	**41.9**
T-Bil (mg/dL)	**1.7**	**4.4**	**6.9**	**2.4**	**1.6**	**1.0**	-	-	-
AST (U/L)	38	56	46	30	28	20	13	16	17
LDH (IU/L)	**396**	**1,390**	**1,893**	**999**	**829**	**227**	**298**	**278**	**222**
BUN (mg/dL)	17.1	33.5	45.6	44.8	36.4	30.2	15.5	15.9	17.2
Cr (mg/dL)	0.90	1.95	2.18	1.86	1.74	1.58	1.27	1.18	1.03
CRP (mg/dL)	11.26	27.73	13.23	4.42	3.63	-	1.07	0.38	0.15
PT-INR	**1.46**	**1.13**	**0.95**	**0.92**	**1.00**	-	**0.96**	-	**0.97**
APTT (s)	49.2	56.7	50.4	34.5	34.7	-	29.9	-	30.4
FBG (mg/dL)	165	277	385	-	385	-	461	-	-
AT III (%)	**84**	**53**	**72**	**88**	**106**	-	**107**	-	-
FDP (mg/dL)	**106.4**	**494.3**	**26.7**	**17.7**	**21.1**	-	**9.8**	-	**7.4**
Schistocyte	−	−	+	+	+	+	+	−	−

Figure 1. Clinical course, treatment, and laboratory data. We applied plasma exchange for thrombotic microangiopathy on days 5-7 and 9-11, and most data improved, such as the platelet count, serum creatinine level, and lactate dehydrogenase level.

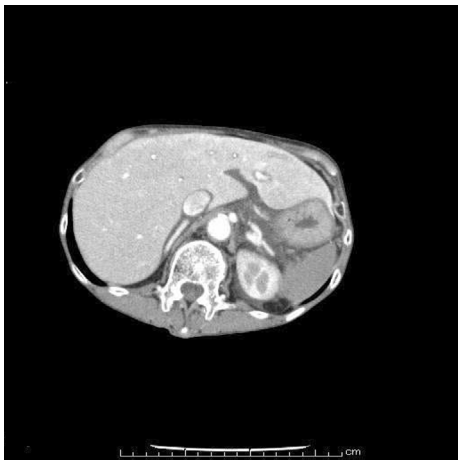

Figure 2. CT revealed hepatomegaly, non-enhancement of the spleen, and lower gastrointestinal tract edema.

Contrast-enhanced computed tomography (CT) revealed complete non-enhancement of the spleen, suggesting splenic infarction (Fig. 2).

We diagnosed her with severe sepsis complicated with 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 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

Table. A Review of Sepsis Case Reports of *Capnocytophaga canimorsus* Complicated 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 MFIPC Crystalline PC	Steroids PE	Survive
8	1991	49/Male	none	splenectomy	not measured	IPM	none	Survive
9	1996	53/Female	Dog lick	heavy smoker	not measured	PCG NTL	Steroids PE HF Ventilation	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 OFLX	PE HDF	Survive
12	2001	66/Male	Dog bite	NA	not measured	CXM MNZ AMPC/CVA	Plasmapheresis HD	Survive
13	2012	72/Male	Dog bite	none	not measured	PIPC/TAZ IMP MEPM	PE	Survive
1	2013	56/Male	Dog bite	splenectomy	not measured	VCM PIPC/TAZ ABPC/SBT	Steroids PE	Survive
6	2016	61/Male	Dog bite	none	39%/ not measured	MEPM CLDM ABPC/SBT	PE CRRT	Survive
7	2018	63/Male	Owned dog	alcoholism	less than 1%/ not measured	CTRX	plasma infusion	Survive
our case		62/Female	Dog bite	none	77.2%/ negative	PIPC/TAZ ABPC AMPC	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: penicillin, PE: plasma exchange, CRRT: continuous renal replacement therapy, HD: hemodialysis, HF: hemofiltration, HDF: hemodiafiltration

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 fibrinogen degradation product (FDP) (Fig. 1). 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 endothelium 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) excessive 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).

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