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【 CASE REPORT 】

Rat Bite Fever Caused by *Streptobacillus moniliformis* in a Cirrhotic Patient Initially Presenting with Various Systemic Features Resembling Henoch-Schönlein Purpura

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Abstract:

We herein report the case of a 61-year-old Japanese cirrhotic patient who developed rat bite fever (RBF) and whose first presentation was serious clinical features mimicking those of Henoch-Schönlein purpura (HSP). In addition to the critical clinical conditions, since the histopathology from purpuric skin eruptions was not inconsistent with that of HSP, therapy with prednisolone was promptly started in order to prevent his death. However, initial blood culture on admission yielded a small and slow-growing bacterial growth, which was gradually revealed by further subculture to be a peculiar bacterium, *Streptobacillus moniliformis*, leading to a definitive diagnosis of RBF. After the immediate cessation of prednisolone, the patient was treated with a more appropriate antibiotic and consequently made a full recovery. An immunocompromised condition with seriously decompensated liver cirrhosis together with moderately severe chronic kidney disease (CKD) in this patient probably exacerbated the severity of the disease.

Key words: rat bite fever (RBF), *Streptobacillus moniliformis*, Henoch-Schönlein purpura (HSP), liver cirrhosis (LC), chronic kidney disease (CKD)

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Introduction

Rat bite fever (RBF) is a rare zoonosis (1) caused by two different bacteria: *Streptobacillus moniliformis* (*S. moniliformis*) and *Spirillum minus* (*S. minus*) (2). These bacteria are transmitted through bite wounds or scratches by rodents, such as rats, and also can be transmitted by the ingestion of contaminated food (oral infection) (3). After a 3- to 10-day incubation period, a variety of systemic symptoms, including a fever, nausea and vomiting, headache, characteristic skin eruptions, polyarthralgia and myalgia, occur (2). Because there is no specific blood test for RBF, a key diagnostic tool is blood culture. Therefore, it is important to consider the existence of this kind of infectious disease and closely examine blood cultures when encountering a pyogenic systemic disease of uncertain cause with purpuric skin eruptions.

We experienced a case of a 61-year-old Japanese cirrhotic patient who developed serious RBF caused by *S. moniliformis* and whose initial clinical presentations resembled those of Henoch-Schönlein purpura (HSP). A close examination of his blood culture revealed the morphological presence of *S. moniliformis* derived from *Rattus rattus,* which was confirmed by subsequent genomic 16S-rRNA sequencing.

Case Report

A 61-year-old Japanese man with a history of alcoholic liver cirrhosis (LC) and positivity for hepatitis C antibody and chronic kidney disease (CKD) was admitted to Tokyo

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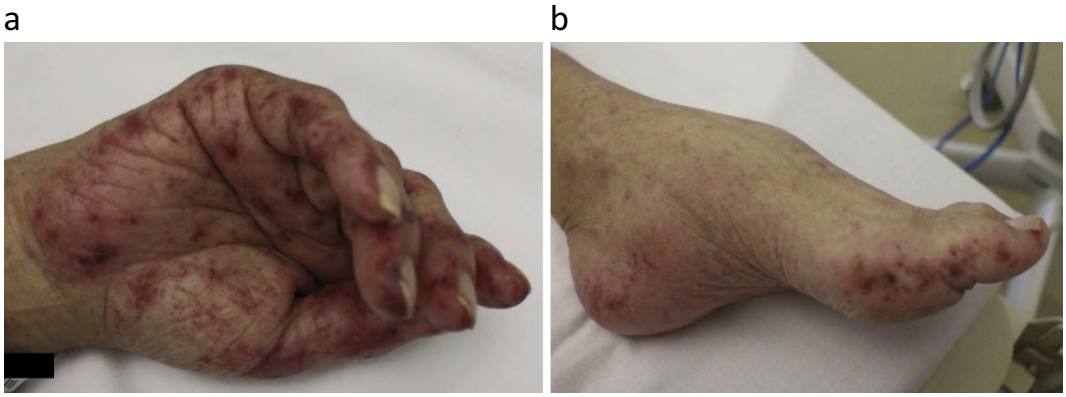

Figure 1. **Dusky-red purpuric skin eruptions were obvious over the patient's palms (a) and soles (b).**

Table 1. **Laboratory Data on Admission.**

Hematology		Biochemistry		Immunology		Urinalysis	
WBC	7,420 /μL	TP	6.6 g/dL	IgG	2,079 mg/dL	pH	5.5
Neu	97.2 %	Alb	1.8 g/dL	IgA	553 mg/dL	SG	1.011
RBC	267×10⁴ /μL	AST	79 IU/L	IgM	122 mg/dL	WBC	3+
Hb	8.8 g/dL	ALT	30 IU/L	C3	42 mg/dL	Nit	-
Hct	25.7 %	LDH	259 IU/L	C4	5 mg/dL	Pro	2+
Plt	3.8×10⁴ /μL	ALP	328 IU/L	CH50	<12.0 U/mL	Glu	-
		T-Bil	1.9 mg/dL	C-ANCA	<1.0 U/mL	Ket	-
Coagulation		D-Bil	1.1 mg/dL	P-ANCA	<1.0 U/mL	Bil	-
PT	40 %	AMY	78 IU/L	Autoantibody	<40		
PT-INR	1.61	BUN	67 mg/dL			RBC	50-99 /HPF
APTT	35.1 s	Cre	4.1 g/dL			WBC	10-19 /HPF
		NH_3	111 μg/dL				
		FBG	101 mg/dL				
		CRP	13.1 mg/dL				

WBC: white blood cell, Neu: neutrophil, RBC: red blood cell, Hb: hemoglobin, Plt: platelet, PT: prothrombin time activity, PT-INR: prothrombin time activity-international normalized ratio, APTT: activated partial thromboplastin time, TP: total protein, Alb: albumin, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, ALP: alkaline phosphatase, T-Bil: total bilirubin, D-Bil: direct bilirubin, AMY: amylase, BUN: blood urea nitrogen, Cre: creatinine, FBG: fasting blood glucose, CRP: C-reactive protein, C-ANCA: cytoplasic anti-neutrophil cytoplasmic antibody, P-ANCA: perinuclear anti-neutrophil cytoplasmic antibody, SG: specific gravity, Nit: Nitrile salt, Pro: protein, Glu: glucose, Ket: Ketone, Bil: bilirubin

Yamate Medical Center following a 7-day history of a fever, headache, diarrhea and fatigue. Six days prior to admission, the patient also noticed skin eruptions developing on his palms (Fig. 1a), soles (Fig. 1b) and knees. His usual clinical data were as follows: serum albumin (Alb), 2.3 g/dL (normal value, 4.1-5.1); serum total bilirubin (TB), 2.2 mg/dL (normal value, 0.2-1.2); prothrombin time activity (PT), 38% (normal value, >70%), serum creatine (Cr), 1.8 mg/dL (normal value, 0.6-1.1); estimated glomerular filtration ratio (eGFR), 32.1 mL/min, indicating Child-Pugh grade-C advanced LC and moderately severe CKD. His habitual alcohol abuse was about 60 g/day as ethanol.

On admission, the patient seemed to be somewhat drowsy and showed slurred speech, suggesting the presence of hepatic encephalopathy. He was 166 cm tall, and his body weight could not be measured due to an impaired gait and balance. His blood pressure was 136/74 mmHg, pulse rate was 120 /min and body temperature was 38.2℃. His heart and lung sounds were normal and the abdomen was slightly distended due to ascitic fluid. Dusky-red purpuric skin eruptions were apparent all over his palms, soles and knees (Fig. 1).

Regarding his laboratory data on admission (Table 1), a complete blood count showed anemia, thrombocytopenia and an elevated proportion of neutrophils, although the white blood cell count was within the normal range. Liver function tests revealed decompensated liver cirrhosis, with a reduced level of serum albumin (Alb), elevated liver enzymes (AST, ALT), elevated total and direct bilirubin, elevated NH_3, and prolonged PT. The renal dysfunction had also significantly progressed (serum creatinine from 1.8 mg/dL to 4.1 mg/dL in just 5 days). Red blood cells, white

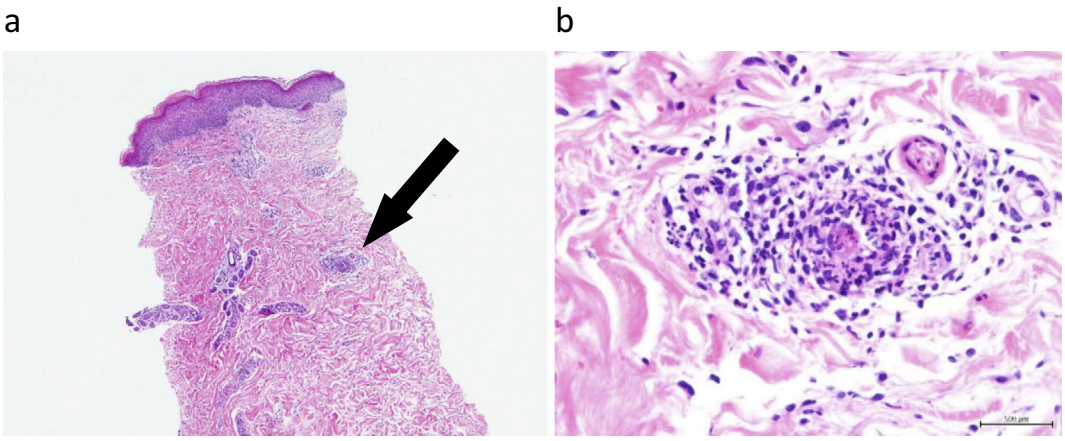

Figure 2. Histopathological findings of a specimen obtained from eruptions on the left knee demonstrated unspecific vasculitis; extravasation of neutrophils and leukocytoclastic vasculitis were noted throughout the dermis (a, b). (a) Hematoxylin and Eosin (H&E) staining 40×, (b) H&E staining 400×.

blood cells were found on a urinalysis. Further close evaluation revealed serum hypergammaglobulinemia: IgG, 2,079 mg/dL; IgA 553 mg/dL and IgM, 122 mg/dL. Serology for anti-hepatitis C antibody was positive. Computed tomography of the abdomen demonstrated surface irregularities of the markedly atrophied liver, splenomegaly and ascetic fluid, suggesting advanced LC.

On the third hospital day, the patient complained of pain in both knees and shoulders; however, X-ray revealed no abnormalities in the joint cavities. Based on his initial clinical symptoms, including a high fever and diarrhea, a presumptive diagnosis of some acute infectious enteritis was made at first, and ceftriaxone sodium (CTRX) 1 g/day was started after performing blood and fecal culture. Simultaneously, the presence of HSP was also suspected because of the purpuric skin eruptions, serum IgA elevation, renal dysfunction accompanied by occult blood in the urine and suggestion of multiple arthritic joints. Based on the severely ill condition of this patient with miscellaneous clinical features, the need for a prompt diagnosis and treatment urged us to perform a skin biopsy on the third hospital day. The histopathological findings of a specimen obtained from eruptions on the left knee demonstrated unspecific vasculitis, and extravasation of neutrophils and leukocytoclastic vasculitis were noted in the dermis around small vessels (Fig. 2). Since Henoch-Schönlein purpura could not be excluded based on the findings of the skin biopsies at that time, 40 mg/day of prednisolone (PSL) was initiated. A renal biopsy was not performed because of his bleeding tendency.

Small and slow-growing bacteria were detected in the anaerobic culture bottle at 33 hours after starting incubation (Fig. 3a). After further subculture by exchanging the media for blood agar, highly pleomorphic filamentous Gram-negative bacilli were isolated on the sixth hospital day (Fig. 3b and c). Based on the morphology of the isolated bacteria and the clinical course, *S. moniliformis* infection was highly suspected. As shown in Table 2, because the isolate was susceptible to ampicillin, CTRX was changed to ampicillin sodium-sulbactam sodium (ABPC-SBT) 3 g/day, and PSL was reduced promptly. By continuing with the antibiotics, his clinical condition improved, and the joint pain of the extremities disappeared. The punctate purpuric skin eruptions on his palms and soles became small pustules and later scabs. The patient was discharged on the 34th hospital day (Fig. 4).

A genotyping approach was attempted by sequencing the bacterial 16S rRNA region. The strain was assigned to the genus *Streptobacillus*, with 98.62% sequence similarity to the type strain of *S. moniliformis* derived from *R. rattus* (Fig. 5).

Discussion

RBF is a rare infectious disease and has been recognized as a zoonosis since ancient times (1). RBF was first reported in the United States in 1839. In the early 1990s, 2 outbreaks of RBF occurred, and more than 200 cases have been reported in that country (4). RBF can be caused by two different bacteria: *S. moniliformis* and *S. minus* (2). *S. moniliformis,* an intraoral resident flora in some rodents, is an aerobic or facultative anaerobic, Gram-negative, highly pleomorphic, filamentous, nonmotile and non-acid-fast rod (2) and is transmitted through bite wounds and scratches by rodents, such as rats; it can also be transmitted via the ingestion of contaminated food (oral infection) (3), causing systemic disease. However, it is not spread from one person to another. In Streptobacillary RBF, subsequent to a 2- to 10-day incubation period (1), a variety of symptoms, such as a fever (92%), nausea and vomiting (40%), headache (34%), skin rash (61%), polyarthralgias (66%) and myalgias (29%), occur (2). Skin manifestations present as measles-like erythematous papules that develop primarily over the extremities, palms and soles, and they are sometimes associated with pustules or purpura. Migratory arthralgia is a classical symptom of Streptobacillary RBF, although it is attributed to an asymmetrical pyogenic infection of multiple

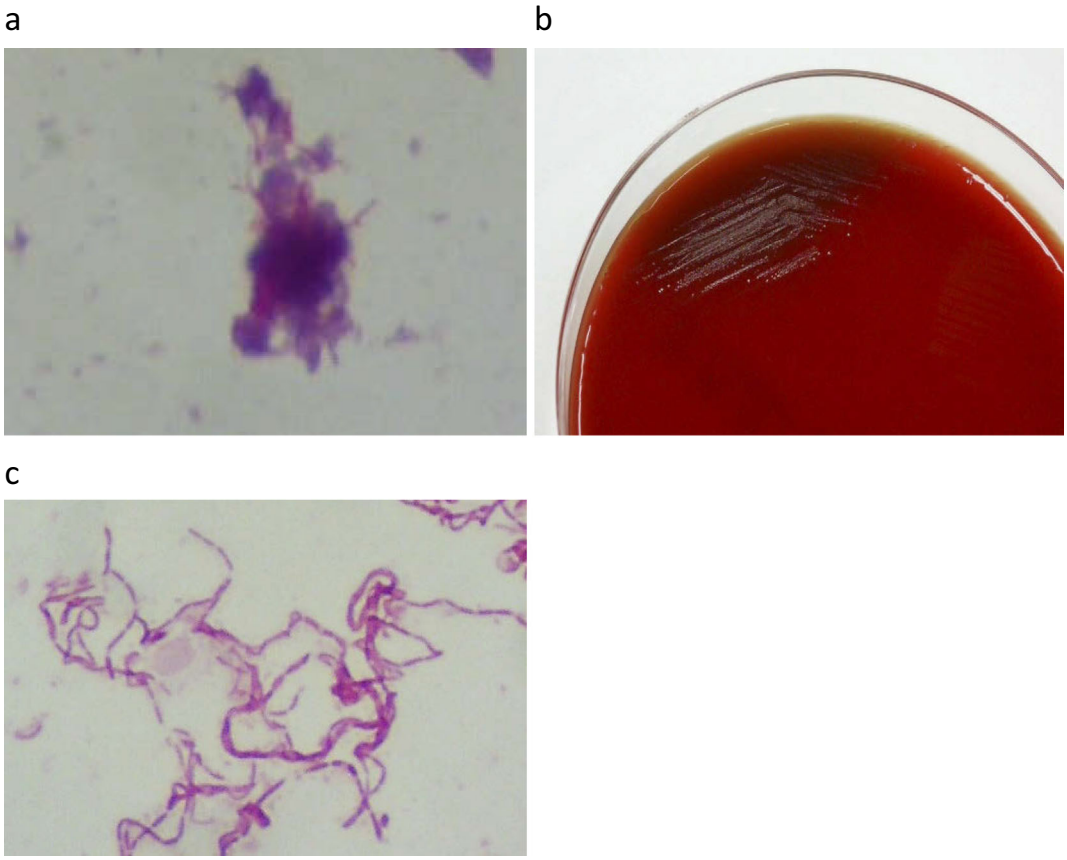

Figure 3. **Small and slow-growing bacteria were detected in the anaerobic culture bottle after 33 h of incubation (a). Gram stain (1,000×). After further subculture by exchanging media, some colonies were visualized on blood agar (b). On the sixth hospital day, highly pleomorphic filamentous Gram-negative bacilli were isolated (c). Gram stain (1,000×).**

Table 2. **Antimicrobial susceptibility for *Streptobacillus moniliformis*.**

antimicrobial agent		MIC (μg/mL)
ABPC	Ampicillin	≤0.12
S/A	Sulbactam/Ampicillin	≤0.5
CEZ	Cefazolin	≤0.5
CTM	Cefotiam	≤0.5
FMOX	Flomoxef	≤0.5
CMZ	Cefmetazole	≤0.5
CPR	Cefpirome	≤0.5
PAPM	Panipenem/Betamipron	≤0.12
LVFX	Levofloxacin	≤0.5
MINO	Minocycline	≤1
CLDM	Clindamycin	≤0.25
ABK	Arbekacin	16
GM	Gentamicin	4
EM	Erythromycin	4
VCM	Vancomycin	≤0.5
TEIC	Teicoplanin	≤0.5

MIC: minimum inhibitory concentration

joints (2). In some reports, about 1 in 10 rat bites may cause Streptobacillary RBF (4), and approximately 7-13% of untreated cases are fatal (2), so the early diagnosis and appropriate treatment are essential for Streptobacillary RBF.

In the present case, RBF caused by *S. moniliformis* developed in the patient who had long-standing chronic diseases with Child-Pugh stage-C LC together with CKD. An immunocompromised condition due to these illnesses was thought to have caused the RBF in this patient to become so severe.

It is important to recognize that blood cultures are sometimes negative in cases of RBF, and other methods, such as PCR, gas-liquid chromatography and 16S-rRNA sequencing, should be considered to confirm these organisms (4). In addition, because RBF is quite rare in Japan today, it is difficult to diagnose upon the first encounter with this disease. Fortunately, in the present case, small and slow-growing bacteria were detected in the anaerobic culture bottles at 33 hours into incubation (Fig. 3a), and highly pleomorphic filamentous Gram-negative bacilli were isolated after further subculture by exchanging media on the 6th hospital day (Fig. 3b and c). Based on the morphology of the isolated bacteria and the clinical course, *S. moniliformis* infection was highly suspected. The possibility of RBF by *S. moniliformis* led us to ask the patient about his history of contact with rats, revealing that the patient had lived in a simple inn located in Shinjuku-ku with unsanitary living conditions, and he had often witnessed rats in his room. A close examination revealed no bites or scratch wounds on his body.

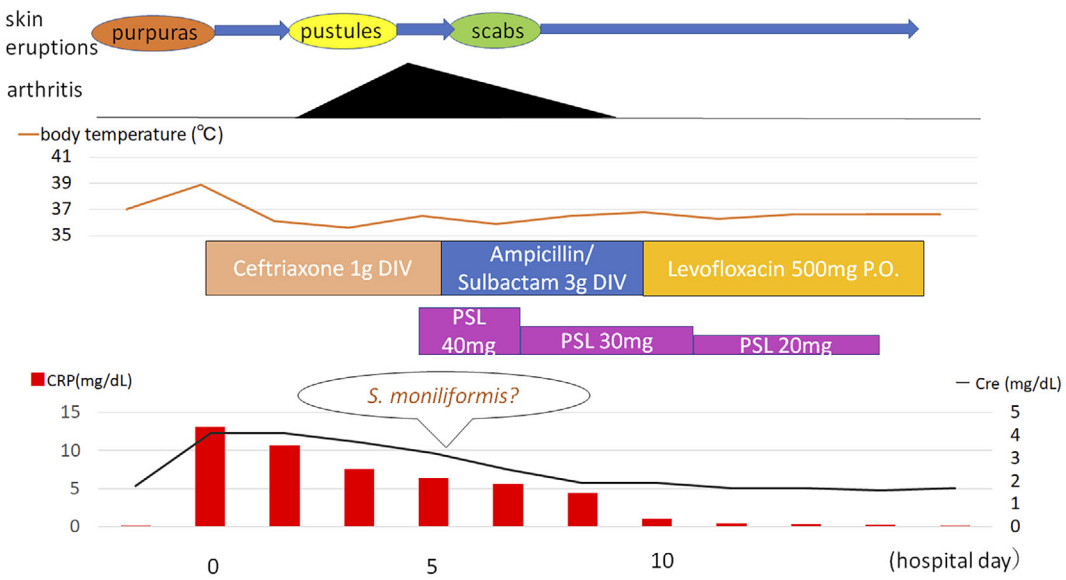

Figure 4. **The clinical course in the present case. PSL: prednisolone, CRP: C-reactive protein, Cre: creatinine**

Streptobacillus moniliformis
Sequence: rRNA-16S ribosomal RNA
Identities=sequence: 1438/1453 (98.96%)
GATGAACGCTGACAGAATGCTTAACACATGCAAATCTATGT**TAATT**ATGTAAGCTTG
CTTA**G**ATA**AGAG**ACATGGTGGACTGGTGAGTAACGTGTAAAGAACTTACCTCTTAG
ACTGGGATAACCATTAGAAATGATGGATAATACTAGATATTATTAG**A**AGT**G**GGCATC
TACT**T**TTAATGAAAGGAGAGATTGCTAAGA...

Figure 5. **The underlined nucleotide sequence was identical to that of the *R. rattus*-derived strain.**

Given the presence of initial gastrointestinal manifestations, oral infection by ingestion of food contaminated by rodents was suspected in the present case.

According to the review by Kimura et al., a sequence analysis of the 16S rRNA gene of *S. moniliformis* suggested that at least two different subtypes were present (5). In addition, *Rattus norvegicus* and *R. rattus* might harbor different types of *S. moniliformis* strains. Since the underlined nucleotide sequence was identical to that of the *R. rattus*-derived strain, the *S. moniliformis* in the present case was concluded to be from *R. rattus* (Fig. 5).

The initial presumptive diagnosis in the present case was HSP accompanied by some kind of infectious disease. The clinical features of RBF resemble those of HSP, including the presence of a fever, purpuric skin eruptions, arthralgia and abdominal manifestations. High serum concentrations of IgA and acute renal deterioration were also observed in this case. Given the severely ill condition, the need for a prompt diagnosis and treatment urged us to perform a skin biopsy.

Typically, the histopathological findings of HSP are leukocytoclastic vasculitis of small vessels associated with the deposition of IgA and C3 immune complex (6). Although the light microscopic findings of the skin biopsy in this case were not inconsistent with those of HSP, the vascular deposits of IgA and C3 in the shallow and mid-dermis specific to HSP could not be confirmed by a subsequent direct immunofluorescence analysis. In addition, inflammatory cell infiltration is observed only in the upper dermis around small vessels in cases of typical HSP histology; however, in the present case, inflammatory cell infiltration was observed not only in the upper dermis but also in the deep dermis around small vessels and sebaceous glands (Fig. 2). The serum high IgA concentrations and acute renal dysfunction in the present case were thought to be due to his habitual alcohol abuse and dehydration induced by his febrile condition and diarrhea. Given the above findings, the involvement of HSP in this case was unlikely.

There are a number of febrile diseases accompanied by purpuric skin eruption, including hemolytic uremic syndrome and thrombotic thrombocytopenic purpura; however these diseases were able to be ruled out because of the absence of elevation of LDH, indirect-type dominant hyperbilirubinemia and schistocytosis suggestive of hemolytic anemia.

We did not initially suspect RBF in this patient. Because RBF is rare disease and its diagnosis is difficult, being aware of the existence of this kind of disease and the characteristic skin eruptions shown in RBF are a key clue to its diagnosis.

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

References

1. Nei T, Sato A, Sonobe K, Miura Y, Takahashi K, Saito R. *Streptobacillus moniliformis* bacteremia in a rheumatoid arthritis patient without a rat bite: a case report. BMC Res Notes **8**: 694, 2015.
2. Elliott SP. Rat bite fever and *Streptobacillus moniliformis*. Clin Microbiol Rev **20**: 13-22, 2007.
3. Wullenweber M. *Streptobacillus moniliformis*--a zoonotic pathogen. Taxonomic considerations, host species, diagnosis, therapy, geographical distribution. Lab Anim **29**: 1-15, 1995.

4. Miraflor AP, Davallow Ghajar L, Subramaniam S, et al. Rat-bite fever: an uncommon cause of fever and rash in a 9-year-old patient. JAAD Case Rep **1**: 371-374, 2015.
5. Kimura M, Tanikawa T, Suzuki M, et al. Detection of *Streptobacillus* spp. in feral rats by specific polymerase chain reaction. Microbiol Immunol **52**: 9-15, 2008.
6. Feldmann R, Rieger W, Sator PG, Gschnait F, Breier F. Schönlein-Henoch purpura during pregnancy with successful outcome for mother and newborn. BMC Dermatol **2**: 1, 2002.