CASE REPORT

Rat-bite fever: An uncommon cause of fever and rash in a 9-year-old patient

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INTRODUCTION

Rat-bite fever (RBF) is most commonly caused by *Streptobacillus moniliformis* and is usually transmitted by a bite or close contact from a colonized rat. Less often, RBF may be transmitted by ingestion of contaminated food or water.[1,2] The disease is characterized by relapsing fever, migratory polyarthritis, and a rash that often involves the extremities, including the palms and soles.[3,4] The diagnosis of RBF is challenging, as clinical and laboratory findings are nonspecific. We report a case of a 9-year-old girl presenting with intermittent fever and nonspecific symptoms who was ultimately diagnosed with RBF via a novel method.

CASE STUDY

A 9-year-old, fully immunized girl presented with 7 days of fever; anorexia; nonbloody, nonbilious vomiting; and diarrhea. She had a widespread, nonpruritic eruption over her trunk and limbs. The patient had oral ulcers and complained of significant muscle and joint pain. Her review of systems was otherwise negative. Her mother reported no sick contacts or recent travel. Her medical history was significant for attention deficit hyperactive disorder and cognitive and speech delays, for which she was taking sertraline, guanfacine, melatonin, vitamin C, and omega-3. Family history was negative for inflammatory bowel disease and autoimmune or rheumatologic diseases.

Abbreviations used:

bp: base pair
PCR: polymerase chain reaction
RBF: rat-bite fever

Her vital signs on presentation were notable for a fever of 39.3°C, tachycardia (heart rate, 123 beats/min), normal blood pressure, respiratory rate, and oxygen saturation. Examination found an ill-appearing, irritable, obese girl with widespread papules and pustules on erythematous bases located over her palms, soles, face, trunk (Fig 1, *A*), and upper and lower extremities (Fig 1, *B* and *C*). There were 2 small, shallow, oval ulcers on her tongue and buccal mucosa. She had no swelling, warmth, or erythema over any joint or muscle group but was unable to walk because of lower extremity pain. The rest of her examination was unremarkable.

She was admitted to the pediatric hospitalist service for workup and management. Her laboratory values were a leukocytosis of 16.97 × $10^3/\mu$L (reference range [ref], 4.5-14.0 × $10^3/\mu$L) with 83.8% neutrophils (ref, 33.0%-73.0%) and 7.1% lymphocytes (ref, 22.0%-57.0%). Hemoglobin was 11.6 g/dL (ref, 11.5-15.5 g/dL), hematocrit was 33.6% (ref, 35.0%-45.0%), and platelets were 422 × $10^3/\mu$L (ref, 145-370 × $10^3/\mu$L). Her total creatinine kinase was 99 U/L (ref, 0-400 units/L), erythrocyte sedimentation rate was 64 mm/h (ref, 0-20 mm/h), and C-reactive protein was 146 mg/L (<3 mg/L). A

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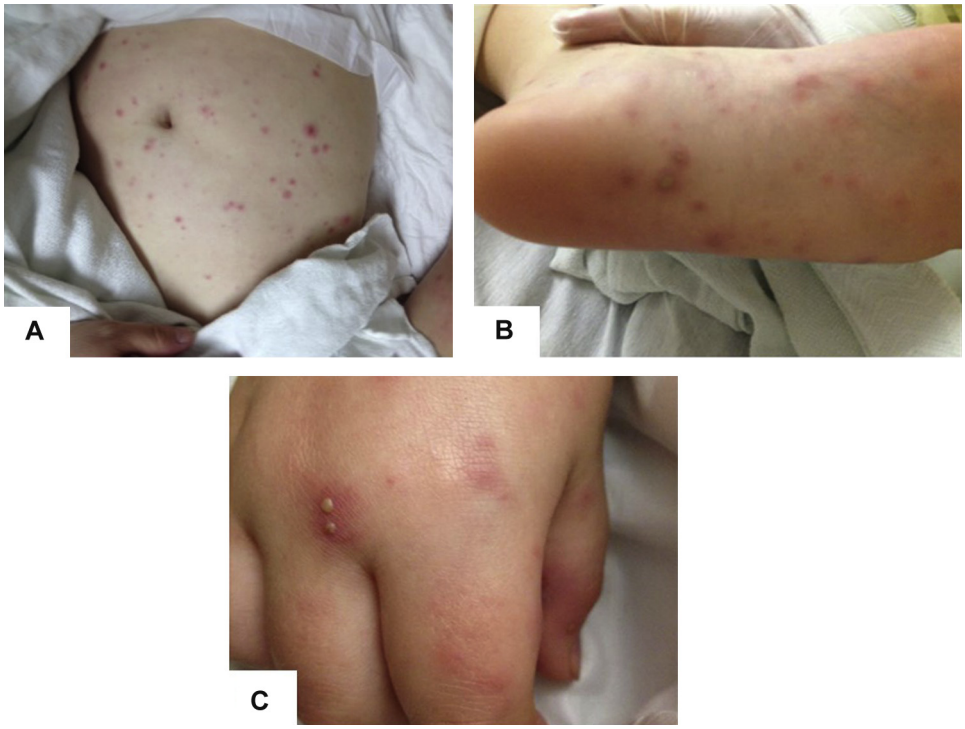

Fig 1. **A**, Erythematous papules on the abdomen. **B**, Purpuric pustules on the sole of the left foot. **C**, Pustules on erythematous bases on the right dorsal hand.

complete metabolic panel was normal. Urinalysis was unremarkable. Blood, urine, and stool cultures were obtained.

Supportive care was provided, and the dermatology service was subsequently consulted. Despite these measures, the patient did not clinically improve. Additional history was obtained by the consulting service, revealing that the patient owned pet rats that had just delivered a new litter. The patient also said that she had been recently playing and kissing the pet rats. Given her clinical presentation and additional history of considerable time handling pet rats, RBF was highly suspected. The dermatology team unroofed a pustule and obtained a skin biopsy, and intravenous penicillin therapy was initiated.

HISTOPATHOLOGIC FINDINGS

A punch biopsy from the right thigh found focal epidermal necrosis, a dense superficial and deep perivascular neutrophilic infiltrate with fibrinoid change of the vessel wall, and extravasation of erythrocytes, consistent with leukocytoclastic vasculitis (Fig 2, *A* and *B*). Rare gram-negative filamentous structures were identified in a small vessel, morphologically compatible with *S moniliformis* (Fig 2, *C*). Other histochemical stains (periodic acid–Schiff, Grocott's methenamine silver, and acid-fast bacilli) were negative for microorganisms.

This diagnosis of RBF was subsequently confirmed by polymerase chain reaction (PCR) of the biopsied tissue, which was positive for *S moniliformis*. Blood, urine, and stool cultures were normal. As her fevers subsided, her oral intake, rash, myalgias, and arthralgias improved. After 3 days of intravenous penicillin and continued clinical improvement, she was transitioned to oral penicillin for 14 days and discharged home. The patient reported complete resolution of symptoms after a week of follow-up.

MOLECULAR FINDINGS

The remaining tissue was sent for PCR analysis after the patient was discharged. PCR analysis was performed on genomic DNA isolated from the formalin-fixed, paraffin-embedded tissue of this skin biopsy. Per Boot and colleagues,[5] the length of the amplified product is 296 base pair (bp) for *S moniliformis*. The enzyme Bfa I cuts the 296 bp *S moniliformis* amplicon to generate 3 fragments of 128 bp, 92 bp, and 76 bp.[5] The undigested and digested PCR products were analyzed by electrophoresis using a 2% agarose gel and the Experion analyzer.

Both the agarose gel (Fig 3, *A*) and the Experion (Fig 3, *B*) showed a single band in the patient sample of 296 bp before digestion with Bfa I. After digestion, the patient sample had all 3

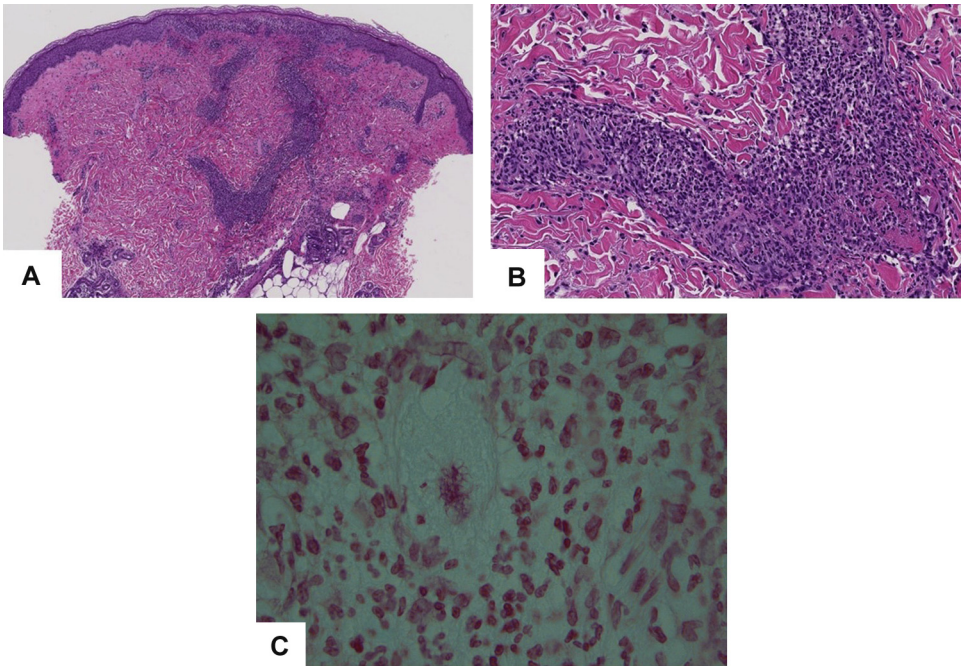

Fig 2. Histologic changes of the skin biopsy. **A**, Focal epidermal necrosis, dense superficial and deep perivascular inflammatory infiltrate. **B**, Dense perivascular neutrophilic infiltrate with fibrinoid change of the vessel wall, consistent with leukocytoclastic vasculitis. **C**, Gram-negative filamentous organisms identified within a small-sized blood vessel. (**A**, Hematoxylin-eosin stain; original magnification: ×40; **B**, Hematoxylin-eosin stain; original magnification: ×200; **C**, Gram stain; original magnification: ×1000.)

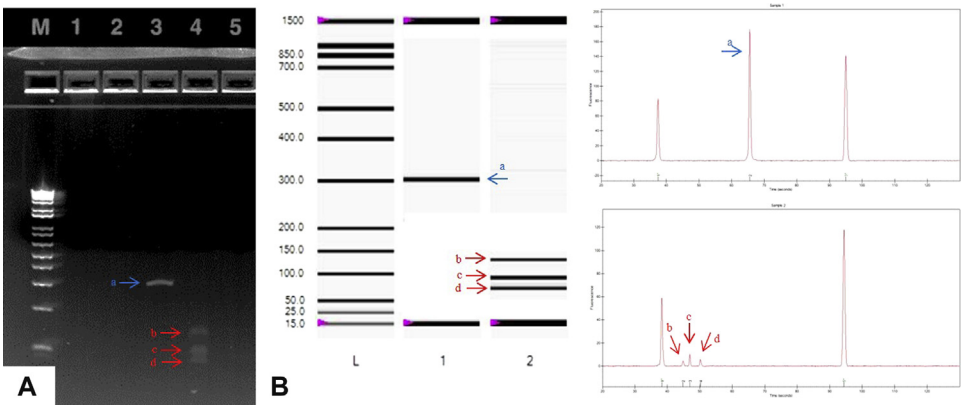

Fig 3. Molecular analysis of the undigested and digested PCR products. Blue arrow and blue *a* represent the undigested PCR amplicon (296 bp). Red arrows and red *b*, *c*, and *d* represent the digested PCR amplicon (72 bp, 93 bp, 130 bp, respectively). **A**, Agarose gel image containing negative control (1-2) and patient sample (3-4). Wells 1 and 3 represent the undigested PCR amplicon, and wells 2 and 4 represent the digested amplicon. **B**, Automated electrophoresis image (Experion) shows the undigested PCR amplicon (well 1), and the digested PCR amplicon (well 2).

fragments previously described (130 bp, 93 bp, and 72 bp), consistent with the presence of *S moniliformis*. A tissue sample known to be negative for the bacteria was used as a negative control.

DISCUSSION

RBF was first reported in the United States in 1839. In 1914, the bacterial pathogen was identified as *S moniliformis*, a filamentous, gram-negative, nonmotile and non–acid-fast rod.[3,4] In the early

1990s, 2 outbreaks of RBF occurred and more than 200 cases have now been documented in the country. Approximately 50% to 100% of wild rats harbor *S moniliformis* in their respiratory tract.[3] About 1 in 10 rat bites may cause infection,[6] and approximately 13% of untreated RBF illnesses are fatal.[3] Because of its low incidence and high mortality, little information exists regarding its pathogenesis.[3]

As the name suggests, this condition may be transmitted by a rat bite, but illness may also be transmitted via close contact with rat urine and feces. Fever, malaise, headache, vomiting, and diarrhea are followed by an eruption of macules, papules, and purpuric vesicles or pustules, with acral accentuation. Migratory arthritis or arthralgias are classical symptoms of RBF, which can be attributed to an asymmetrical pyogenic infection of multiple joints causing streptobacillary septic arthritis.[7] Oral ulcerations have not been reported in association with RBF in the literature. Delayed diagnosis of RBF may be responsible for severe complications such as endocarditis, myocarditis, encephalitis, and visceral abscesses.[3]

The differential diagnosis of fever, acral papulopustular rash, and arthralgias in an immunocompetent child include both systemic infections and inflammatory conditions. Lesions of chronic meningococcemia may be pustular and purpuric and are accompanied by fever and arthralgias. If there is concern for sexual abuse, disseminated gonorrhea and secondary syphilis should also be considered. Rocky Mountain spotted fever is characterized by fever, headache, and malaise followed by erythematous macules on the hands and feet, which may become purpuric or pustular.

Coxsackievirus infection may also present with fever, oral erosions, widespread edematous papules, and vesicopustules involving the hands, feet, perioral skin, and buttocks. Persistence of rash after 10 days argues against coxsackievirus in this case, as does the pustular (rather than vesicular) quality and location of the lesions. Varicella zoster virus lesions are vesicular rather than pustular and heal within 1 to 2 days with scarring. Noninfectious inflammatory conditions that should be considered include acute generalized pustular psoriasis, acute generalized exanthematous pustulosis, leukocytoclastic vasculitis, and bowel-associated dermatosis/arthritis syndrome.

In this case, biopsy of a pustular skin lesion showed leukocytoclastic vasculitis and gram-negative filamentous structures identified in a small blood vessel, confirming the clinical suspicion of RBF. Similar histologic findings have been described in patients with RBF[2,3,8]; however, to our knowledge, *S moniliformis* bacilli have not been identified previously on histologic tissue sections.

It is important to recognize that blood cultures are often negative in cases of RBF, and other methods such as PCR, gas-liquid chromatography, and rRNA sequencing may be considered to detect these organisms. Sodium polyanethol sulfonate, which is present in aerobic blood culture media at many institutions, can inhibit the growth of *S moniliformis* and lead to false-negative blood cultures.[7]

To our knowledge, this is the first reported case in which organisms characteristic of *S moniliformis* were identified on histologic tissue sections by Gram stain with further confirmation by PCR. Owners of pet rats should wear gloves, wash hands, and avoid touching their mouth after coming into contact with rats or cleaning their cages. They should also seek immediate medical care after having symptoms consistent with RBF.[6,9] Clinicians should be aware of this diagnosis when the exposure history is suggestive, as the symptoms can be variable and nonspecific. Early treatment with antibiotics is crucial to avoid progression to later stages and disease complications.

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