Case Report

Rat-Bite Fever Presenting with Rash and Septic Arthritis

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Rat-bite fever is an uncommon disease known for its endemicity to occur worldwide. Although most patients tend to develop mild symptoms with improvement from conventional antibiotics, it can progress with severe complications with a mortality rate as high as 13% without proper treatment. The authors report a complicated case of rat bite-fever involving a 61-year old woman who presented with fever, petechial rash, and septic arthritis following a rat bite. Initially, multiple antibiotics were administered but were not effective. As a consequence, invasive procedures such as arthrotomy and joint debridement were done and prolonged antibiotic was administered until clinical resolution. Since many cases do not have a history of rat bite and may present with fever, rashes, and arthritis it is essential to distinguish it from other diseases. Here, the authors will provide details on the etiology, clinical manifestations, diagnosis, and management to aid prompt detection and treatment of the disease.

Keywords: *Rat-bite fever, Haverhill fever, Sodoku fever*

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Rat-bite fever is an uncommon zoonotic disease as a result of bites or contact by secretions or feces from rats, rodents, squirrels, weasels, or animals that prey on them[1,2]. The infection is attributable to either *Streptobacillus moniliformis* or *Spirillum minus*, which are anaerobic, nonmotile, pleomorphic gram-negative bacilli and gram-negative spirochetes, respectively. Although it exists worldwide, the former is more common in Europe and America, while the latter is encountered more often in Asia[2]. The true incidence remains unknown, humans are more frequently exposed to these animals in laboratories, as pets, and in the wild. The disease they carry encompasses three distinct clinical disorders, namely rat-bite fever ("sodoku"), streptobacillary rat-bite fever, and Haverhill fever[1]. Rat-bite fever can easily be recognized by clinicians, identified in the laboratory, and treated with appropriate antibiotics if suspected. However, inappropriate care, delay in disease recognition without effective antibiotics can lead to complications and a mortality rate as high as 13%[2]. In 1994 Buranakitjaroen P. et al reported rat-bite fever in Thailand, and recently the CDC has identified rat-bite fever in the Unexplained Death and Critical Illnesses (UNEX) project in 2003 and stressed the importance to consider the disease in acutely ill patients with reported rat exposure[3,4]. The authors report a case of rat-bite fever with a typical history and clinical presentation, but lack of laboratory confirmation.

A 61-year-old female retired nurse from Thailand was referred to Phramongkutklao Hospital due to a history of fever with myalgia and arthritis of both knees, wrists, and fingers for 4 days after a rodent bit her right thumb. Initially she took erythromycin and ibuprofen (Brufen®), and was prescribed rabies vaccination and tetanus toxoid. Three days later she began experiencing fever with chills and myalgia. The following day the patient developed additional symptoms of symmetrical polyarthritis involving the wrists, knees, fingers, and ankles, mimicking rheumatoid arthritis. She had concurrent petechial rashes over her face, palms and soles and was eventually admitted to a nearby hospital. Investigations for infectious causes and rheumatoid arthritis were performed while antipyretics and 4 mg of dexamethasone every 6 hours were administered. For four consecutive days,

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her condition deteriorated so she was referred to Phramongkutklao Hospital. She had underlying dyslipidemia and had been on gemfibrozil (Lopid®) for 5 years. In spite of that, she has been healthy and there has been neither history of other medications or food allergies.

Clinical examination revealed a fully conscious febrile female with petechial rashes on her face, both hands and feet. She also had joint erythema, swelling and tenderness of both knees, wrists and both distal and proximal interphalangeal joints. A pansystolic murmur grade II unaccompanied by respiratory symptoms was identified on auscultation while other findings were unremarkable.

The laboratory results were as follows: hematocrit 36%, WBC 10,000 cells/mm^3, PMN 89%, lymphocytes 17%, monocytes 3%, platelets 124,000 cells/mm^3, ESR 93 mm/hr and normal coagulograms. Serum biochemistry, liver function tests, VDRL, ANA profile, rheumatoid factor, LE test, chest radiographs and electrocardiogram were within normal limits. Initial septic work-up including Widal tests, hemocultures, urine cultures and anti HIV were negative. Skin biopsy was done on the right palm on the third day of admission. The results demonstrated a superficial perivascular infiltration of lymphocytes and extravasation of red blood cells without vasculitis. Transesophageal echocar-diography ruled out endocarditis and therapy was initiated with 1.2 gm intravenously every 6 hours of amoxicillin/clavulanic acid (Augmentin®) plus doxycycline 200 mg/day, which resulted in no improvements of symptoms. Septic work-up was repeated and joint aspiration was performed. Neither Gram stains nor acid-fast stains showed any organism. Cultures did not foster any organism growth, however, synovial fluid analysis confirmed infection, with leukocyte counts of over 64,000 cells/mm^3, all of which were neutrophils. The cytological results and abnormal joint X-rays, favored septic arthritis, antibiotics were switched to ceftriaxone (Cef-3®) 1gm intravenously twice daily and 3 million units of penicillin G every 4 hours.

A week passed without recovery except for the absence of rash. Synovial fluid cultures still produced no growth although the patient was still suffering from fever and arthritis. Accordingly, arthrotomy and joint debridement were conducted with synovial tissue collection intended for pathological examination and cultures. But due to technical problems in handling of specimens, only the pathological result of nonspecific severe acute and chronic synovitis was reported. Taking the history of rat bite into account along with the progression of the disease, the authors highly suspected rat-bite fever with septic arthritis, therefore ceftriaxone (Cef-3®) and penicillin G were administered continuously for 4 weeks. The patient responded satisfactorily and was soon discharged upon recovery.

Discussion

Rat bite fever is a rare zoonotic worldwide febrile illness acquired by direct contact with infected rodents or their contaminants. Nasopharyngeal flora carriage rates in laboratory rats range from 10%-100%, whereas those in the wild range from 50%-100%[2,5]. Moreover, rat-bite fever has also been associated with bites, scratches, and licks of mice, squirrels, gerbils and other animals, for instance dogs and cats that prey on them[1,5], and contact with rodent excrements[2]. Ingestion of food, milk or water contaminated with rat feces are also capable of causing bacteremia- so called Haverhill fever[1]. Occasionally complications arise and diagnosis can be difficult especially in cases that do not recall animal contact, or in cases without specific laboratory confirmation. These cases are often not reported and the exact incidence of this disease remains unknown.

The onset of symptoms usually follows rodent exposure by 10 days (usually 2-3 days) if the infection is due to *Streptobacillus moniliformis*. The patient will experience high fever and chills followed by headache, vomiting, myalgia and marked muscle tenderness. Within 2-4 days of fever, ninety percent of the patients will develop rashes which can appear morbilliform, pustular, petechial, or erythema multiforme-like, usually confined to the palms and soles, and twenty percent of the patients will desquamate while resolving. Cutaneous manifestations with cutaneous abscesses has been reported[8-12]. Concomitantly in full-blown infection, over fifty percent of patients experience arthritis with or without joints effusions. Any joint can be affected, but the most commonly involved is the knee[14]. Joint pain usually subsides within 3 weeks of antibiotics but can end up destructed. While all symptoms tend to resolve, relapses are common and complications such as meningitis, endocarditis, myocardits, pneumonia, and fulminant sepsis can occur and attribute to death [1,2,5,6,13,14].

On the other hand, if the disease source is from *Spirillum minus*, the incubation period is 1-4 weeks but the onset of symptoms would be earlier. In contrast to the *S. moniliformis*, local reaction from

the bite wound infected with *S. minus* is more striking but arthralgia is rare. The site of trauma is characterized by induration and tenderness, which can eventually ulcerate into a chancre-like lesion with prominent lymphadenopathy and lymphangitis[2,5,15]. The skin rashes appear as large reddish-brown macules that can be either generalized or localized. In rat bite fever there is usually leukocytosis, with or without thrombocytopenia or coagulopathy, and a 25% false positive VDRL[7]. Gram staining of the blood, abscess or joint fluid will support diagnosis in the absence of a rodent bite. Unfortunately, *Spirillium minus* cannot be cultured. Hence it must be detected by darkfield examination of clinical materials or serological tests. In the absence of a history of rodent exposure, the clinical diagnosis of rat-bite fever as in the presented case, would be problematic.

Rat-bite fever must be differentiated from infections such as Rocky Mountain Spotted-fever, meningococcemia, disseminated gonococcal infection or other zoonosis, viral infections e.g. rubella, parvovirus B19, coxsackie, and autoimmune diseases like rheumatoid arthritis, Reiter s syndrome, and vasculitis[5]. The history of animal contact, pattern of rash, disease progression, identification of the causative agent by staining, serology, immunohistochemical assays and 16S rRNA gene sequence amplification from DNA extracted from paraffin tissue samples could aid in ruling out other diseases[6,7,16].

Penicillin is usually considered the drug of choice, although penicillin resistant strains have been reported[6]. For example, *Streptobacillus moniliformis*, one of the agents responsible for rat-bite fever, also manifests the L-form, the cell wall deficient variants which are resistant to penicillin[13]. Ampicillin, tetracycline and second and third generation cephalosporins are alternative agents[6,17]. There are also reports of successful treatments from erythromycin[18] and a combination of penicillin and chloramphenical[10]. In cases with septic arthritis, treatment includes arthrotomy, drainage and joint larvage in addition to antibiotics [13]. In the presented case, the clinical course correlates with that of rat bite fever although septic work up produced negative results. There have been many factors contributing to our fruitless yield. First, the patient had been partially treated with antibiotics prior to specimen collection. Second, *S. moniliformis* is a highly pleomorphic Gram negative rod, which may stain positively on Gram stain and is often dismissed as a proteinaceous debris because of its numerous bulbous swellings with occasional clumping (moniliformis means necklace-like)[2,7]. Third, the slow growth rate, the fastidious growth requirements of the organism and inappropriate transport media during the acute phase of illness could have impeded its growth. For instance, *S. moniliformis* would require media enriched with blood, serum or ascitic fluid for growth[6]. The addition of even small amounts of the anticoagulant present in blood culture tubes (sodium polyanethol sulfonate) can interfere with its growth[19]. Here the culture media tubes contained this substance, which hampers *S. moniliformis'* germination. Moreover, the bacteria possess variable positivity of Gram stains and their structures are inconsistent[6,9,16]. Furthermore, even with the appropriate media, the organisms themselves might not grow. Even when arthritis is involved, the

Fig. 1 Erythema, swelling and tenderness of the metacarpal and phalangeal joints

Fig. 2 Erythema, swelling and tenderness of the metatarsal joint Petichiae involving both feet

joint fluid is typically sterile. Likewise, identification of the organisms from culture requires a reference laboratory to perform subcultures and biochemical tests[4]. Lastly, serological test is not yet available.

When rat-bite fever can not be ruled out, septic work up should include Gram stains, dark field examination of the infected specimen, and silver staining of the tissue biopsied, and bacteria cultures[16]. Culturing should be done meticulously by collecting blood or synovial fluid in tubes without sodium polyanethol sulfonate and incubated into media supplemented with 20% solution of sterile normal rabbit serum and incubated in a humid environment with 5%-10% CO_2 at 98.6 $^{\circ}$F (37 $^{\circ}$C) for $\geq$ 5 days[16]. So alerting the bacteriology laboratory of the diagnosis before obtaining cultures will aid greatly in producing positive colonies. Inoculating the specimen directly in a hemoculture bottle would not yield.

As the human population incessantly increases, so does exposure to animals, enabling many vulnerable to rare zoonotic diseases[20]. Prevention of severe disease might depend on increasing the awareness of appropriate risk-reduction activities and possible symptoms of rat-bite fever among persons who have exposure to rats. Although definite diagnosis is crucial, rapid laboratory confirmation of infection with *S. moniliformis* might not be possible. Being easily treatable but potentially lethal with 10%-15% mortality rates in healthy adults, rising even to 53% in rare cases with cardiac involvement with perior endocarditis[2,6,14]. The authors hope that the details provided on the etiology, clinical presentation, investigations, and treatment will bring familiarity of rat-bite fever among clinicians so prompt diagnosis and treatment could be achieved in patients with compatible clinical presentation and risks.

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โรคไข้หนูกัดที่มาด้วยผื่นและข้ออักเสบติดเชื้อ

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โรคไข้หนูกัดเป็นโรคที่พบไม่บ่อยแต่มีการกระจายทั่วโลก ผู้ป่วยส่วนใหญ่มักมีอาการไม่รุนแรง และตอบสนองดีต่อการรักษาด้วยยาปฏิชีวนะธรรมดา ยกเว้นในบางรายที่อาจเกิดภาวะแทรกซ้อนได้ ในรายงานนี้ขอนำเสนอผู้ป่วยโรคไข้หนูกัด หนึ่งราย เป็นผู้ป่วยหญิงอายุ 61 ปี มาพบแพทย์ด้วยเรื่องไข้ มีผื่นเป็นจุดเลือดออกเล็กๆ ร่วมกับมีอาการอักเสบ ติดเชื้อที่บริเวณข้อ หลังจากที่ถูกหนูกัด ผู้ป่วยได้รับการรักษาด้วยยาปฏิชีวนะหลายชนิดแต่อาการไม่ดีขึ้น จึงให้การรักษาโดยการทำผ่าตัดที่ข้อและเลาะเอาเนื้อเยื่อที่ตายออกร่วมกับการให้ยาปฏิชีวนะเป็นระยะเวลานานจนอาการหายเป็นปกติ เนื่องจากผู้ป่วยโรคไข้หนูกัดบางรายอาจไม่มีประวัติถูกหนูกัดนำมาก่อนแต่จะมาพบแพทย์ด้วยเรื่องไข้, ปวดข้อและผื่นที่ผิวหนังคล้ายกับอาการของโรคอื่นๆ ได้หลายโรค ในรายงานนี้จึงได้ทบทวนถึงสาเหตุ อาการแสดง หลักเกณฑ์การวินิจฉัยและรักษาเพื่อช่วยให้แพทย์สามารถวินิจฉัยและรักษาโรคนี้ได้อย่างทันท่วงที