Rat Bite Fever Human Disease

45

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ABSTRACT

Rat Bite Fever is an emerging and re-emerging zoonotic disease that occurs in periodic, endemic, and epidemic forms. It is an acute, febrile, and systemic disease classically characterized by acute relapsing fever, rashes, migratory polyarthritis which affects the hands, wrists, and knees. In 1926, in Haverhill, Massachusetts, a large bacterial outbreak was reported by Place and Sutton, caused by the contamination of milk products with Streptobacillus moniliformis (S. moniliformis) bacteria. This outbreak was named Haverhill fever. It is an infrequent disease transmitted by rats and its causative agents are two specific types of bacteria that generate two different kinds of illnesses such as Spirillosis and Streptobacillosis. S. moniliformis bacteria are geographically present only in North America (Streptobacillary Rat Bite Fever) whereas Spirillum minus (S. minus) bacteria that is only reported in Asia and causing Spirillary Rat Bite Fever. It is also called Sodoku in Japanese which means rat poison (So= rat and doku= poison). Both bacterial species are common in rats and can be transmitted from rats to humans through urine, nasal passages, feces, or eye excretions of an infested rat. However, sometimes the infection is spread through food contaminated with excretions such as feces and urine. Specialized culture conditions or PCR tests are usually used for the diagnosis of Rat Bite Fever. Treatment with Tetracycline and Penicillin is commonly used for Rat Bite Fever. If not treated, its mortality rate is 10% to 13%, and a 53% mortality rate with endocarditis in some cases. In order to decrease the risk of infection, when an individual has been bitten by a rat, the affected area should be thoroughly washed and cleaned with disinfected as soon as possible.

Keywords: Spirillum minus, Streptobacillus moniliformis, Rat Bite Fever, Rat, zoonotic disease.

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1. INTRODUCTION

Rat Bite Fever is an emerging and re-emerging zoonotic disease that occurs in periodic, endemic, and epidemic forms (Pal 2005; Pal et al. 2021). It is an acute, febrile, and systemic disease classically characterized or manifested by acute relapsing fever, rashes, migratory polyarthralgia, or polyarthritis which affects the hands, wrists, elbows, shoulders, and knees (Hudsmith et al. 2001). In 1926, in Haverhill, Massachusetts, a large bacterial outbreak was reported by Place and Sutton, caused by the contamination of milk products with *Streptobacillus moniliformis* (*S. moniliformis*) bacteria. This outbreak was named Haverhill fever (Place et al. 1934). It is an infrequent disease transmitted by rats and its causative agents are two specific types of bacteria that generate two different kinds of illnesses such as Spirillosis and Streptobacillosis (Pal 2007). *S. moniliformis* bacteria are geographically present only in North America [Streptobacillary Rat Bite Fever] (Ogawa et al. 2018) whereas *Spirillum minus* (*S. minus*) bacteria that is only reported in Asia and causing Spirillary Rat Bite Fever, also called Sodok (Fukushima et al. 2018). The majority of the cases are reported in Japan, but specific strains have also been identified in the U.S., Europe, Australia, and Africa. Both bacterial species are common in rats and can be transmitted from rats to humans through urine, nasal passages, feces, or eye excretions of an infested rat. However, sometimes the infection is spread through food contaminated with excretions such as feces and urine. In addition, pets like dogs and cats that come into contact with rats can also be a source of transmission (Eisenberg et al. 2016).

Millions of people around the world are attacked by animals every year. Dogs and cats are being responsible for approximately 90% of these incidents. (Griego et al.1995). Rats are only 1% accountable for these bites (Glaser et al. 2000), and 2% of rat bites lead to Rat Bite Fever. People have long recognized that these bites can cause the disease. Indian physician Wagahbhat treated a cutaneous burn caused by a rat bite in the 2300s years ago (Row 1918). Many spectators consider it to be the first reported case of Rat Bite Fever in India.

For several years, there were significant misperceptions concerning the diagnosis of Rat Bite Fever. Tileston in 1916, Blake as well as Schottmuller 1914 and other researchers, isolated *Streptothrix muris ratti* (*Streptobacillus monliformis*) from the blood of patients bitten by rats with persistent fever, nearly about 100 years ago (Schottmuller 1914). Scientists in Japan believed that the only causative agent of Rat Bite Fever was *Spirochaeta morsis muris* or *S. minus* (Futaki et al. 1916). However, it is now assumed that *S. moniliformis* or *S. minus* are the causative agents of Rat Bite Fever. Rat bite fever is more frequently caused by *S. moniliformis* worldwide and *S. minus* infection is recounted less frequently and primarily this infection is reported in Asia. This infection is known as Sodoku in Japanese which means rat poison (So= rat and doku= poison) (Place et al. 1934; Pal 2007). The diagnosis of *S. monliformis* is challenging because it is a fussy microbe that makes ultimate analysis complicated (Shadrin et al. 2020). Specialized culture conditions or PCR tests are usually used for the diagnosis of Rat Bite Fever (Rovid 2021).

Treatment with Tetracycline and Penicillin is commonly used for Rat Bite Fever (DuBray et al. 2019). If not treated, its mortality rate is 10% to 13% (Zhang et al. 2019), and a 53% mortality rate with endocarditis in some cases (McKee et al. 2013). In order to decrease the risk of infection, when an individual has been bitten by a rat, the affected area should be thoroughly washed and cleaned with disinfected as soon as possible.

2. ETIOLOGY

S. monliformis and *S. minus* are the causative agents of Rat Bite Fever and they are also the source of two distinct types of illness. A comparison of key characteristics and clinical features of Rat-Borne Streptobacillus infection from *S. moniliformis* and *S. minus* has been mentioned in Table 1.

2.1. *STREPTOBACILLUS MONILIFORMIS*

In history, *S. moniliformis* was known by several names such as "*Multiforms*" and "*Asterococcus muris*" by Heilman in 1941 (Heilman 1941). "*Nocardia muris*", "*Actinomyces -muris ratti*" and "*Streptothrix muris ratti*" by Borgan and Gaustad in 1948 (Borgen et al. 1948). "*S. moniliformis* (Levaditi et al. 1925) "*Haverhillia moniliformis*" and "*Proactinomyces muris*" by Parker et al. 1926 (parker et al. 1926), *Actnobacillus muris* by Waterson et al. 1953 (waterson et al. 1953). *S. moniliformis* is most frequently capable of inducing Rat Bite Fever (Rosser et al. 2014). *Streptobacillus notomytis (S. notomytis)* is new species of Streptobacillus that can infrequently cause Rat Bite Fever in humans (Kusuda et al. 2020). *Streptobacillius felis* is another species that is also associated with rat bite infections in humans, in addition to *S. notomytis* (Matt et al. 2021).

2.2. MORPHOLOGY OF *S. MONILIFORMIS*

S. moniliformis can take various forms, including filaments, chains, or curved rods (Paegle et al. 1976). It is a gram-negative, non-motile, extremely pleomorphic, non-acid-fast organism with a rod-shaped appearance. When observed under a compound microscope, it typically appears as a straight line,

Table 1: Comparison of key Characteristics and Clinical Features of Rat-Borne Streptobacillus infection; *S. moniliformis* vs. *S. minus.*

Causative agents	*S. moniliformis*	*S. minus*
Morphology of organism.	Gram-negative, highly pleomorphic, filamentous, chains or curved rod-shaped bacteria with bulbul's swellings.	Gram-negative, tightly coiled, short and thick spiral rod-shaped bacteria.
Geographical distribution.	Worldwide.	Mainly Asia.
Route of Transmission.	Haverhill fever is caused by a rat bite, scrape, mucosal contact, or contaminated food.	Rat bite.
Onset of bite wound healing.	Rapid healing.	At the outset of symptoms, a chancre-like lesion developed but was quickly healing.
Incubation period.	3-10 days.	1-3 weeks.
Signs at the onset of a disease.	Headache, nausea, vomiting, and fever.	Fever, chills, and nausea.
Local signs.	A gentle lymphadenitis.	Localized lymphangitis as well as lymphadenopathy.
Type of Fever or nature.	An irregular or asymmetrical Relapsing fever.	A regular or consistent relapsing fever.
Arrival (Normal).	2-3 days.	2-4 weeks.
Polyarthritis.	Ordinary (reported in 49% of the patients).	Unusual.
Rashes (Eruptions).	Morbilli form to purpurie.	Molecular, often microscopy confluent.
Percentage of effectiveness.	75%.	50%.
Untreated mortality rate.	7-13%.	6.5%.
Complications.	Pneumonitis, prostatitis, pancreatitis, myocarditis, endocarditis, pericarditis, myocarditis, anemia, diarrhea, as well as abscesses in various organs.	Myocarditis, Endocarditis, nephritis, hepatitis, meningitis, and splenomegaly are rare but can occur.
Diagnosis.	Molecular methods, culture. Microscopy.	Diagnosis, molecular methods, culture, microscopy; vaccination of animals
Antibiotics (Drug of choice).	Penicillin.	Penicillin.

although it can sometimes be fusiform and contain several adjacent asymmetrical bulbous or Monilia-like swellings. The bacteria are often organized in chains and may appear somewhat roughly in clusters. Its colonies typically look like a "puff ball or cotton ball". *S. moniliformis* measures 0.3 to 0.7 micrometers in width and 1 to 5 micrometers in length. Filaments and bead-like chains can reach lengths of up to 150 micrometers and may include fusiform swellings that are 1 to 3 micrometers wide (Lambe et al. 1973). *S. moniliformis* exists in two different forms. It is usually present in the bacillary form, but it can also take on the inducible or spontaneous form. The Spontaneous form presents in L form which is cell wall-deficient and appears clustered with a morphological resemblance to "fried eggs". The L form is a nonpathogenic type (Freundt 1956).

2.3. *SPIRILLUM MINUS*

S. minus is another sporadic disease-causing agent related to Rat Bite Fever and is primarily found in the Middle East. It was discovered in the 19th century and initially known by various names, such as "*Leptospiramorsus minor*", "*Spirocheta morsus muris*" or "*Sporozoamuris*", "*Spirochaeta laverani*", "*Spironema minor*". In 1924, it was officially named *S. minus* (Washburn 2005). There is very limited knowledge about the taxonomic relation of *S. minus* (Kusuda et al. 2020).

2.4. MORPHOLOGY OF *S. MINUS*

S. minus is a tightly coiled, short, thick, gram-negative, spiral rod-shaped bacterium with two to six-helix spirals, each approximately 0.2 to 0.5-micrometer diameter (Washburn 1995; Washburn 2005). *S. minus* cannot be cultivated or grown in synthetic media. Dark-field microscopy, Wright stain, or Giemsa stain is used for examining the characteristic features and for the initial diagnosis of Spirochetes (Washburn 2005).

3. HOSTS

3.1. RATS

Rats belong to the primary reservoir of *S. moniliformis,* which is normally present in the commensal flora of the rat's respiratory tract (Eisenberg et al. 2016). Laboratory mice and household pet rats have demonstrated colonization rates ranging from 10% to 100% by *S. monliformis*, while wild rats often exhibit colonization rates between 50% and 100%. Infected rats occasionally show the symptoms of the disease but the majority of the rats are asymptomatic (Paegle et al. 1976).

3.2. MICE

S. monliformis is not commonly found in all strains of mice and in fact, many inbred strains of mice are significantly resistant to streptobacillosis disease. Infected laboratory mice might demonstrate the signs of disease such as polyarthritis, septic lymphadenitis, and multi-organ micro abscesses which can further lead to cachexia, septicemia, and death (Glaser et al. 2000).

3.3. OTHER ANIMALS

Infection and colonization of *S. moniliformis* have been reported in ferrets, pigs, gerbils, cats, and dogs (Torres et al. 2003). Streptobacillary disease has been demonstrated in turkeys and koalas and has also been reported in non-human primates, such as Titi Monkeys (Valverde et al. 2002).

3.4. HUMAN INFECTIVITY

Rat bite fever is a zoonotic disorder that can cause disease in humans (Fox et al. 2007). Rat bite fever, along with rat infestations involving *S. moniliformis* represents a significant public health concern with both physical and pathological implications that leftovers unknown.

4. EPIDEMIOLOGY

In the United States, *S. moniliformis* rarely causes Rat Bite Fever, and only a few cases are reported yearly. From 2000 to 2012, only 17 cases were documented in California (Gupta et al. 2017). *S. moniliformis* is responsible for only 10% of Rat Bite Fever cases in human beings (Etscorn et al. 1987; Hagelskjaer et al. 1998). But nowadays it has become common practice to keep rats as indoor pets in Europe (Royer 2015). As a result, approximately 20,000 rat bite cases occur annually in Europe (Julius et al. 2021). According to ancient studies, people living in poverty are more commonly infected with Rat Bite Fever and 50% of cases are reported in children (Hirschhorn et al. 1999; Josephson 2012). Additionally, pet store workers and laboratory technicians are also at risk because rats have gained popularity as pets and are used as research subjects (King et al. 2021). Pregnant women, immune-compromised individuals, and people over 65 years old are at a high risk. In Asia, the commonly existing bacteria responsible for causing Rat Bite Fever is *S. minus,* which is known as Sodoku (Fukushima et al. 2018). In Japan, in 1979, the *S. notomytis* species was initially secluded from spinifex hopping mice and was further hereditarily studied in 2015. In spite of the fact that neither the illness nor the causative organism is well understood by health officials, over two hundred instances of Rat Bite Fever in the nation. The oldest documented case of Rat Bite Fever was in an 87-year-old male (Torres et al. 2003), while the youngest reported case was a 2-month-old baby (Sens et al. 1989; Elliott et al. 2007).

5. TRANSMISSION

Rat Bite Fever is a zoonotic disease, its causative agent, *S. minus* is directly transmitted by vectors such as rats and mice to individuals primarily through bite or scrape and *S. moniliformis* can be spread through ingestion (Vanderpool et al. 2007). Rat Bite Fever causing bacteria are also observed in dogs, cats, ferrets, and especially in laboratory animals like *Rattus norvegicus* (Norwegian rat) and *Rattus rattus* (Black rat) which are recognized as potential reservoirs of Rat Bite Fever (Gaastra et al. 2009). *S. moniliforms* are commensal organisms normally found in the respiratory flora of rats, as well as in their oral, nasal, and conjunctival secretions and even in the urine of infected animals as shown in Fig. 1 (Elliott et al. 2007). It is estimated that 1 out of 10 rat bites lead to Rat Bite Fever (Hagelskjaer et al. 1998). An individual can acquire the infection through direct contact with a contaminated surface if they have an open wound or mucus membrane. Haverhill fever (epidemic arthritic erythema) can also be transmitted by contaminated food or water with rat's stools. Rat Bite Fever is not a contagious illness and cannot be transferred directly from person to person. Transmission from one person to another person has never been documented.

6. PATHOGENESIS

Rat Bite Fever has a low incidence and a low fatality rate when diagnosed and treated. Therefore, few details are known regarding the pathogenesis of *S. moniliformis*. Morphological abnormalities seen in Rat Bite Fever which are often linked to bacterial diseases include lymph node sinus hyperplasia, interstitial pneumonia, hepatosplenomegaly, endocarditis, and myocarditis as shown in Fig. 2. All of these abnormalities are visible in the autopsy of the Rat Bite Fever patient. Autopsies of Rat Bite Fever patients

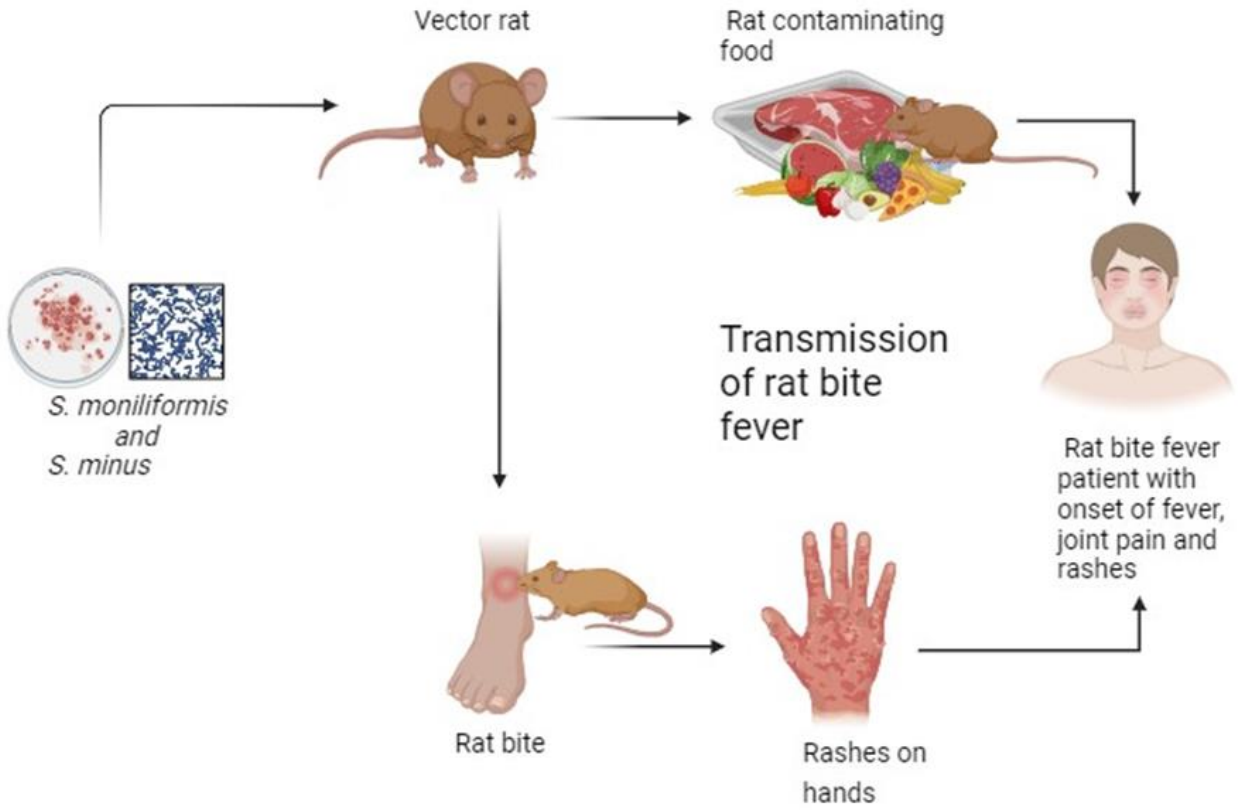

Fig. 1: Transmission of Rat Bite Fever.

have shown degenerative abnormalities in the kidneys and liver. Leukocytoclastic vasculitis was also observed during the skin biopsy of a previous Rat Bite Fever patient (Zhang et al. 2019). Experimental infection in mice causes progressive polyarthritis, which exhibits fibrin purulent exudate in the joint space and nearby periosteal tissue within the first 24 hours of the attack of an etiological agent. By day 4, this condition transforms into a predominantly periarticular abscess, and by day 7, necrosis occurs due to the presence of macrophages. After two weeks, periostitis starts to form, and three weeks later, fibrous connective tissue starts to proliferate. Although the organisms have been removed from the blood, liver, and spleen, it is concerning that they may still be present in joint spaces three months after infection (Elliott et al. 2007). Early attempts must be made to identify potential infections because the signs of Rat Bite Fever match with those of other diseases such as Post-infectious arthritis, Rheumatoid arthritis, Lyme disease, and Hemolytic uremic syndrome.

7. CLINICAL SIGNS

Rat Bite Fever is typically asymptomatic in carrier rats, but secondary bacterial pulmonary infections and abscesses can be absorbed sporadically. The pathogenicity of the disease changes depending on the strain of bacteria in rats, and affected rats may develop prolonged septicemia, leading to sudden death (Pongsuttiyakorn et al. 2021). The typical clinical signs of Rat Bite Fever include weight loss, hemoglobinuria, cyanosis, conjunctivitis, cervical lymphadenitis, and diarrhea. Acute signs of the disease include supportive polyarthritis, osteomyelitis, and abscesses as shown in Fig. 3 (Baker 2003). In humans, Rat Bite Fever caused by *S. monliformis* has been associated with two different clinical syndromes.

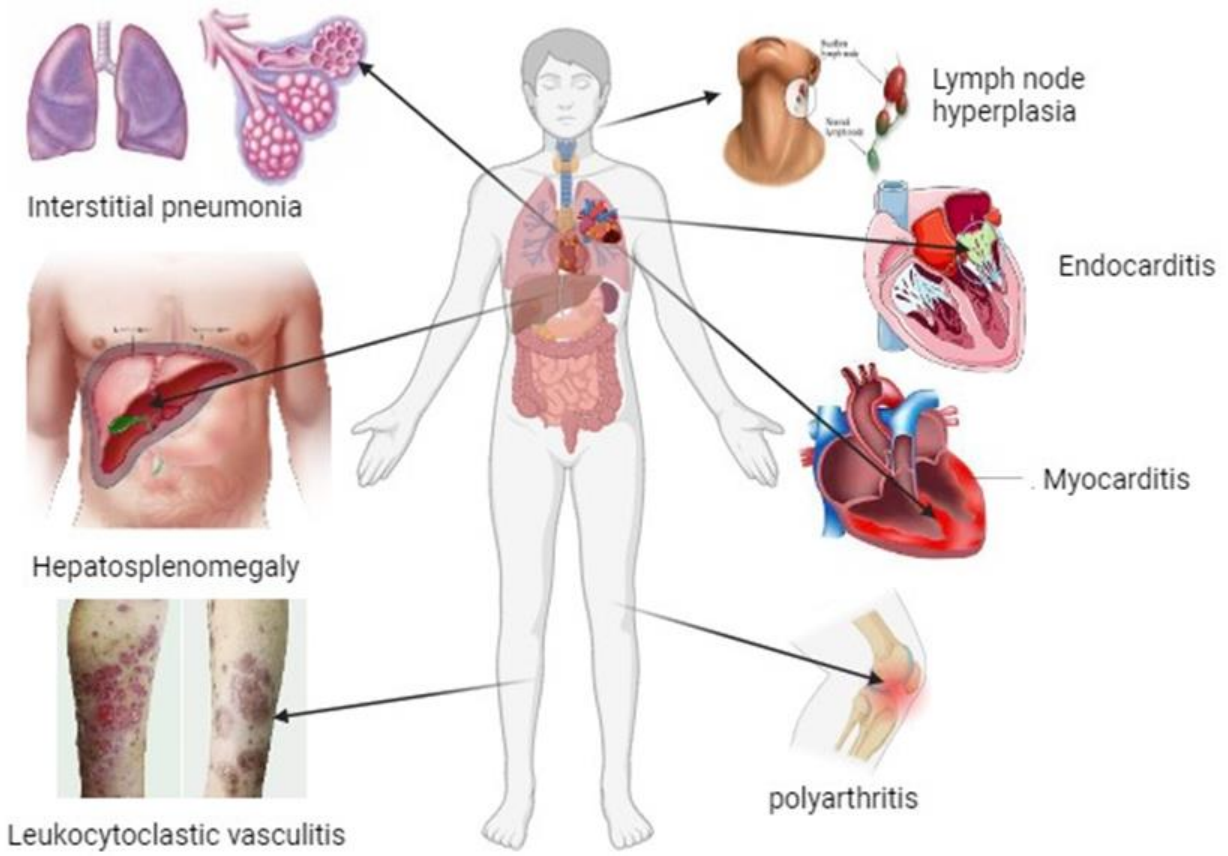

Fig. 2: Pathogenesis of Rat Bite Fever.

Haverhill fever syndrome is one of the outbreaks of epidemic disease that was first reported in 1926 and is contracted by humans as a result of the consumption of milk and food infected with *S. moniliformis*. Patients with Haverhill fever experience symptoms and indications that resemble Rat Bite Fever, but the disease is hallmarked by pronounced vomiting and pharyngitis, with no common temporal and geographic exposure to rats (Abusalameh et al. 2018). On the other hand, the Rat Bite Fever is the more typical syndrome caused by *S. monliformis* bacteria. The symptoms of the disease include a sudden onset of high fever (92%), severe migratory arthralgia (66%), rashes (61%), headaches (34%), sore throat (17%), vomiting (40%) and hepatitis which commonly appears 2-4 days after the onset of infection (Washburn 1995 and Mutters 1999). In some patients, meningitis, endocarditis, hepatitis, and localized abscesses have also been noticed (Elliott et al. 2007; Abusalameh et al. 2018).

The clinical signs of infections caused by *S. notomytis* are characterized by fever, rashes, polyarthritis, hepatitis, meningitis, and spondylodiscitis which are also common (Kusuda et al. 2020; Pongsuttiyakorn et al. 2021). *S. minus* bacteria cause rat bite infections in the Middle East which are referred to as Sodoku. In terms of medical characteristics and geographic distribution, this condition is distinct from Rat Bite Fever. The bite area becomes indurated and develops into an ulcer following a latent period of approximately 14-18 days, often associated with regional lymphadenopathy and fever. There are frequent relapses spaced by 3 to 7-day afebrile intervals. Red, brown, and even black macular rashes arise in around 50% of patients contain plagues. Joint manifestations are rarely seen (Adams et al. 1955; Freels et al. 2004). Cerebrospinal fever, mastoid bone inflammation, Hamman-Rich syndrome, polyarthritis nodosa, sarcoidosis, Idiopathic pericarditis, myocardial inflammation, liver inflammation,

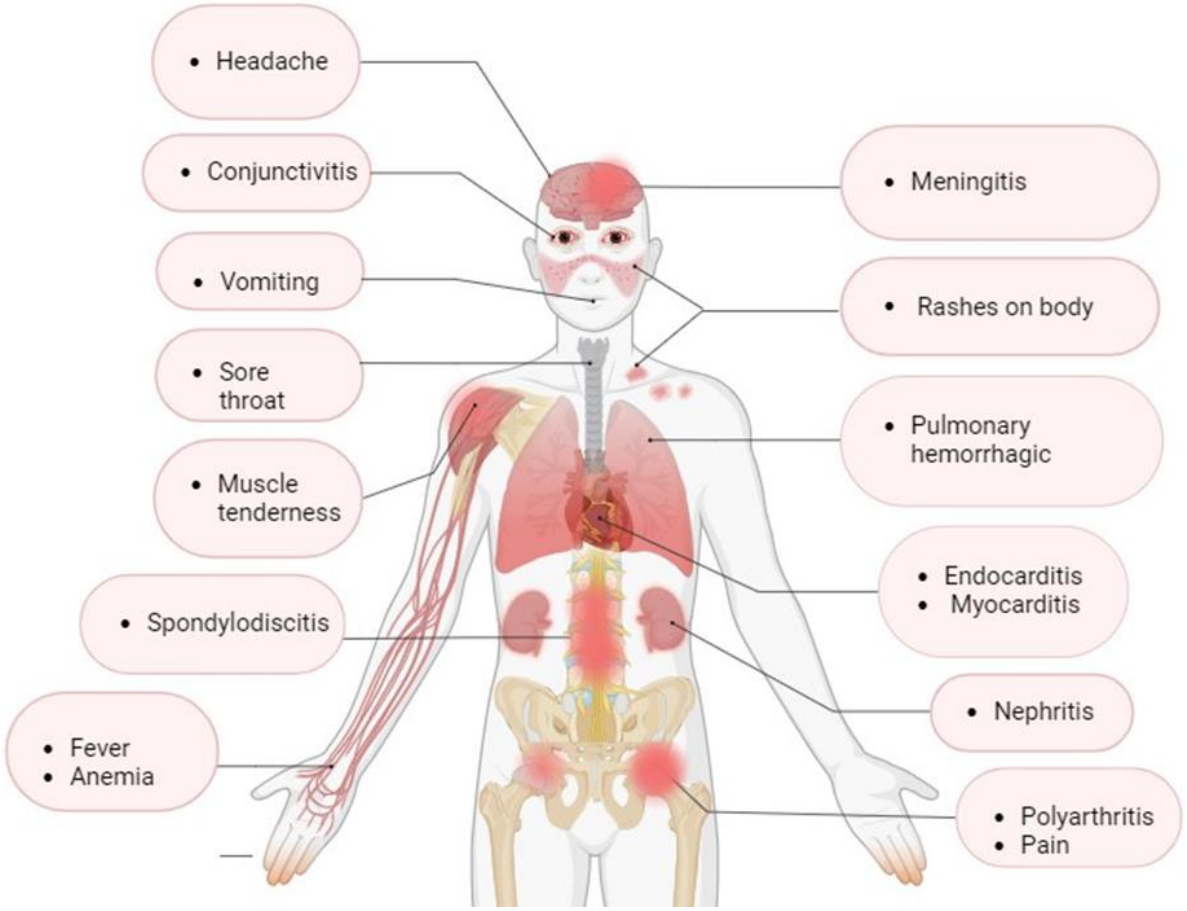

Fig. 3: Clinical Signs of Rat Bite Fever.

prostate pain syndrome, infectious arthritis as well as the development of abscesses in various organs are extensively reported complication of Rat Bite Fever (Abusalameh et al. 2018; DuBray et al. 2019). The Prognosis of infectious endocarditis in addition to Rat Bite Fever is particularly poor, with a 50% fatality rate (DuBray et al. 2019; Pena et al. 2020).

8. HISTOPATHOLOGIC FINDINGS

An L2-L3 spinal disc aspiration procedure, under CT guidance, was carried out for histopathology and culture analysis. Gram-negative rods become visible in gram-staining. The histopathological showed discitis-like fibrocartilage with degenerative alterations and acute inflammation. Histopathology of vertebral disc's fibro-elastic cartilage indicates that Rat Bite Fever may be the potential cause of osteomyelitis and discitis (Eisenberg et al. 2016; Abusalameh et al. 2018). A 9-year-old girl, who had received all of her vaccinations, was discovered to have Leukocytoclastic vasculitis, which is characterized by dense perivascular neutrophil infiltration, fibrinoid changes in the arterial wall, and localized epidermal necrosis. This was observed through a deep and superficial influx of dense perivascular neutrophils in the punch biopsy of her right thigh. *S. monliformis* extremely pleomorphic, filiform structures, were identified as gram-negative, rod-shaped, non-motile, non-acid-fast bacteria within a little vessel and identified using Gram staining (Elliott et al. 2007). Additional histochemical stains, include Grocott's and silver methylamine, acid-fast bacilli, and periodic acid Schiff) were negative for microorganisms.

9. HISTOLOGICAL LESIONS

There is a significant lack of knowledge about the histological lesions associated with Rat Bite Fever in humans. Observations have been conducted using animal models to better understand the disease process. In affected rats, the histological lesions associated with Rat Bite Fever vary depending on the stage of infection and the organ involved. Commonly affected organs include the skin, joints, heart, liver, lungs, and spleen. A few histological lesions that have been studied in animal models are given below.

9.1. SKIN

At the site of a rat bite or scratch, inflammatory changes can be noticed, which may include the infiltration of immune cells such as neutrophils and lymphocytes. These changes can be accompanied by necrosis and ulceration of the skin (Abusalameh et al. 2018).

9.2. JOINTS

Arthritis is a common feature of Rat Bite Fever. The affected joints show synovial hyperplasia, inflammatory cell infiltration, pannus formation (proliferation of granulation tissue), and destruction of articular cartilage (Abusalameh et al. 2018; DuBray et al. 2019).

9.3. HEART

Histological examination of the heart involved myocarditis which is characterized by infiltration of inflammatory cells into the myocardium. This condition can lead to the necrosis of cardiac muscle fibers and the presence of inflammatory cells such as lymphocytes and macrophages (Abusalameh et al. 2018; DuBray et al. 2019).

9.4. LIVER

Inflammation of the liver or hepatitis can also be absorbed in the case of Rat Bite Fever. Histologically, this condition is characterized by necrosis of the focal area, infiltration of inflammatory cells, and congestion of blood vessels (Abusalameh et al. 2018; DuBray et al. 2019).

9.5. SPLEEN

Inflammation of the spleen (splenitis) can also be absorbed in case of Rat Bite Fever. This condition includes the infiltration of immune cells, congestion of blood vessels, and destruction of splenic architecture (Abusalameh et al. 2018).

9.6. LUNGS

Pulmonary lesions in Rat Bite Fever can alter and may include intestinal pneumonia, bronchopneumonia, or abscess formation. Necrosis and congestion of blood vessels can be absorbed in the affected lungs (Abusalameh et al. 2018; DuBray et al. 2019).

10. DIFFERENTIAL DIAGNOSIS

In recent studies, the Rat Bite Fever infection has shown strong similarities to other infections that are detected during the incubation period. These similarities include a triplex pattern of fever, rheumatoid

symptoms, and rashes on various parts of the body, during the period of definitive analysis and in the period of symptom remission (Onodera et al. 2020; Shadrin et al. 2020. Note that, the distinction between these common symptoms of Rat Bite Fever is wide-ranging (Raffin et al. 1979; Raffin et al. 1979; Ojukwu et al. 2002; Freels et al. 2004). Rat bite fever can be differentially diagnosed from microbial sepsis caused by *streptococcus pyogenes* and *Staphylococcus aureus*, as well as from dispersed gonorrhea and meningococcemia. Furthermore, it can be differentiated from *Streptococcus pyogenes*-related diseases such as Lyme disease, ehrlichiosis, brucellosis, post-streptococcal reactive arthritis, rheumatic fever, scarlet fever, and rheumatic fever (Rordorf et al. 2000). In endemic areas, rickettsial infections like Rocky Mountain Spotted fever must be considered. Rat Bite Fever also shows a resemblance to spirochetal infections such as secondary syphilis and leptospirosis. Venereal disease laboratory tests (VDRL) are perceived to be false positive in 50% of the Rat Bite Fever patients. Some viral infections, such as *Parvovirus* B19 and *Espteinbarrvirus* are noticeable and confused with Rat Bite Fever. Relapsing fever can also confuse the Rat Bite Fever with malaria, typhoid fever, and Borrelia recurrentis. Non-infectious diseases that are somewhat similar to Rat Bite Fever are collagen vascular disease and drug reactions (Kimura et al. 2008).

11. DIAGNOSIS

The diagnosis of Rat Bite Fever can be complex due to several reasons, such as lack of knowledge, the involvement of multiple contributory agents, and a multitude of complications. To diagnose Streptobacillus infection, serology, organism isolation or molecular methods can be used. Among these methods, the molecular method, PCR is considered highly sensitive and more accurate for diagnosing *S. moniliformis* infection in Rattus species (Van Nood et al. 2005; Gaastra et al. 2009; Eisenberg et al. 2016). The confirmation of *S. moniliformis* by molecular method (PCR) has been more frequently reported (Chean et al. 2012). Medical confirmation in humans is typically attained through the culture of blood, joint puncture, or liquor cerebrospinal (Van Nood et al. 2005; Irvine et al. 2006; Gaastra et al. 2009). However, this method is not suitable due to the slow growth of the bacterium (Hagelskjaer et al. 1998). *Streptobacillus* bacteria are fastidious, making the culture of *S. moniliformis* or *S. notomytis* difficult (Madhubashini et al. 2013). Confirm Rat Bite Fever diagnosis can be quite challenging. If *S. moniliformis* or *S. notomytis* is suspected as the underlying cause, plasma, synovial fluid, or aspirates of abscesses should be injected into bacteriological media that lack sodium polyanethol sulfonate (SPS), such as anaerobic culture media. Sodium polyanethol sulfonate which is a common component of aerobic blood culture media may limit the growth of *S. moniliformis* or *S. notomytis* and thus provide indications of low negative prognostic values (Lambe et al. 1973; Washburn 1995). The gold standard diagnostic method used in the laboratory for isolating the causative agent from specimens like blood, synovial fluid, or abscess aspirates. However, even with the proper diagnostic tests, in cases of simple disease, synovial fluid cultures might be negative because the etiology of polyarthritis could be related to an immune-mediated response, which essentially means that it's a somewhat real disease involving the human body. The negative organic responses such as peroxidase, phosphate, fumarate, and amidohydrolase might be inadequate for detecting *S. moniliformis* in the majority of medical research laboratories (Joshi et al. 2010).

Reliable serological tests are not available for diagnosis of *S. moniliformis*. However, various alternative tests, such as gas-liquid chromatography, PCR, rRNA sequencing, and 16SDNA sequencing, have been found to be more sensitive than culture for detecting *S. moniliformis* (Miraflor et al. 2015; Eisenberg et al. 2016). It’s important to note that using regular blood samples for these kinds of tests is not permitted. The bacterium *S. minus* cannot be cultivated in artificial media. Dark-field, Phase contrast preparations, Wright, Giemsa, or silver staining are the principal techniques used for microbiological diagnosis and identifying the typical morphology of causative organisms. Using dark-field microscopy, spirochetes can be diagnosed in the blood of these animals after 4–15 days. However, there is no serological or molecular (PCR) testing

available for *S. minus* due to the inability to culture this bacterium. (Washburn 1995). Therefore, it is advisable to conduct further research to develop immunological and molecular techniques for the diagnosis of *S. minus* infection or Spirillosis.

12. TREATMENT

Rat Bite Fever is often treated with Penicillin G, which is also the drug of choice for this infection (DuBray et al. 2019). The recommended dose of Penicillin G for adults is 400,000–600,000 IU per day intravenously (IV) for 7–14 days. If there is no response to the antibiotic within 24 hours (two days), the dosage may be raised to 1.3 million IU orally. Ceftriaxone is also advised for the treatment of Rat Bite Fever infection, typically for a duration of two weeks. The adult dose rate for Ceftriaxone is 1.5 to 2 g per day (Zhang et al. 2019). In the case of children, treatment usually begins with Beromycin at a dose of approximately 3 grams per day, administered in four divided doses for the first seven days. Afterward, intravenous Penicillin G is recommended at a dosage of 20,000 to 50,000 IU/ kg of body weight per day (equivalent to 15 to 29 mg/kg/day), for the first five to seven days. Patients with Penicillin allergies can also be treated with Doxycycline and oral Tetracycline (Gaastra et al. 2009).

S. moniliformis is also exquisitely sensitive to multiple antibiotics, including Ceftriaxone, Clindamycin, Tetracycline, Erythromycin, Cephalosporin, and Vancomycin. It is also somewhat vulnerable to aminoglycosides, fluoroquinolones, and Chloramphenicol (Edwards et al. 1986; McKee et al. 2013; Shadrin et al. 2020). However*, S. moniliformis* shows resistance to Trimethoprim-Sulfamethoxazole, Polymyxin B, and Nalidixic acid (Rygg et al. 1992; Wullenweber 1995). In the case of Rat Bite Fever without any complications, treatment can typically be completed within two weeks. However, if Rat Bite Fever is complicated by endocarditis, a longer course of treatment is required. This may involve an overdose of Penicillin G in combination with either Gentamicin or an Aminoglycoside in a dual treatment approach (McCormack et al. 1967; Torres et al. 2003). If the isolate is sensitive to the concentration of 0.1 g/ml, the recommended dosage for adults is 4.7 million IU/day (equal to 4.8 grams) of Intramuscular (IM) Procaine Penicillin G. For adults, if the isolate is more resistant, they should receive 20 million IU/day (equal to13 grams) of intravenous (IV) Penicillin G (Rupp 1992). Children should be administered a dosage of 96 to 144 mg/kg (equal to 150,000 to 250,000 IU/kg/day).

Arthroscopy or Joint lavage and arthroplasty are recommended for managing the localization of disease inside the joints, especially in case of septic arthritis of large joints. Arthroscopy is preferred over arthrotomy because it is less intrusive than arthrotomy, this is especially important for pediatric patients because it allows for direct examination and observation of joint structure, as well as an assessment of the level of demolition or destruction that may have occurred. Additionally, it enables the evaluation of any potential disturbance in the ongoing development of children (Donatto 1998). Surgical intervention is significant in decreasing the bacterial burden within the joint and facilitating local drainage to eliminate any infections present in the affected joint.

13. PREVENTION AND CONTROL

The occurrence of Rat Bite Fever can be reduced by various measures. Firstly, the municipal or public environments should be kept free from rats, where accidental contact with rats is the most predominant source of transmission. The Public should be careful about consuming contaminated food and water such as unpasteurized milk (Graves et al. 2001). Individuals should properly sanitize and wash their hands after any direct contact with rats. Applying antiseptic and following prophylactic chemoprophylaxis after any scratch (Pal 2007). The protective measures should be followed by laboratory employees, pet store

workers, and those working with sewage. It's important to avoid handling wild rats, whether dead or living (Walker et al. 2019). Furthermore, if Rat Bite Fever is suspected in Lab workers, pet store employees, and owners of pets must obtain emergency medical attention (Shadrin et al. 2020). Antibiotic therapy should begin as soon as possible to reduce the illness's development and consequences (Onodera et al. 2020).

14. PROGNOSIS

Bacterial endocarditis due to Streptobacillary infection has a predominantly poor prognosis, with death rates of 60% (DuBray et al. 2019; Pena et al. 2020). The prognosis of Streptobacillary septic arthritis is superior when all patients are treated without experiencing long-term complications (Rupp 1992).

15. CONCLUSION

Rat Bite Fever is a relatively unappreciated disease that can have potentially serious consequences, including a 10% mortality rate. This disease typically presents with a sudden onset of fever, joint pain, and rashes. It is transmitted through a rat bite or contact with a rat's saliva, urine, and feces. However, humans can also ingest excreta through water and contaminated foods, such as raw milk. One significant challenge in diagnosing Rat Bite Fever is its nonspecific and variable symptoms, especially in patients with no prior history of animal exposure. Molecular diagnosis becomes necessary, particularly when there is no suspicion of exposure to rats or their excretions. Clinicians need to maintain awareness of this diagnosis when the patient's history of exposure is suggestive, as the symptoms are nonspecific and can be variable. Early diagnosis and rapid treatment with antibiotics are essential to prevent the disease from progressing to more severe stages and disease complications. Further investigation is needed to better understand the pathophysiology, and epidemiology of Rat Bite Fever.

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