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Case report

A case of atypical cat scratch disease with bone and joint infection diagnosed through clinical metagenomics

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ABSTRACT

Cat scratch disease (CSD) is a common zoonotic infection caused by *Bartonella henselae* (*B. henselae*) and typically presents with fever and regional lymphadenopathy. However, skeletal involvement, including osteomyelitis and arthritis, is rare. We report a 28-year-old immunocompetent female who presented with a five-month history of persistent right knee swelling without fever or lymphadenopathy. She had previously undergone distal femoral tumor resection with prosthetic joint replacement, and this episode of chronic knee swelling together with the imaging findings was highly suggestive of prosthetic joint infection. Approximately one month before the onset of knee swelling, she had sustained a scratch from a cat. Conventional microbiological tests, including joint effusion and drainage fluid cultures, were negative. Metagenomic next-generation sequencing (mNGS) of joint effusion identified *B. henselae* with 27 specific sequence reads, 0.1 % genome coverage and an RPM ratio of 1.9. This result was subsequently confirmed by a quantitative PCR assay targeting the *nuoG* gene. The patient underwent surgical debridement followed by oral minocycline and rifampin for 8 weeks, resulting in marked clinical improvement. This case underscores that *B. henselae* infection should be considered in culture-negative bone and joint, particularly prosthetic joint, infections with a history of cat exposure, and that mNGS can provide valuable etiological evidence in atypical CSD.

Introduction

Bartonella spp. are gram-negative, facultative intracellular bacteria classified within the class Alphaproteobacteria, order Rhizobiales, and family Bartonellaceae. Historically, they were placed in the α2-subgroup of Proteobacteria [1]. In recent years, it has been widely recognized that most *Bartonella* species can be transmitted directly or indirectly between different host species via arthropod vectors [2,3]. Among them, *Bartonella henselae* (*B. henselae*) is one of the most notable pathogens and is widely distributed worldwide [4].

Cats serve as the primary reservoir of *B. henselae*, transmitting the bacterium to humans through scratches, bites, or cat fleas [2]. Human infection with *B. henselae* can result in cat scratch disease (CSD), a common zoonotic disease with diverse clinical manifestations [4]. Typical CSD is characterized by fever and localized lymphadenopathy, and most often affects immunocompetent children and adolescents [5,6]. However, atypical or disseminated forms are more frequently observed in immunocompromised individuals [4,7,8]. Despite the widespread occurrence of *B. henselae* infections, their diagnosis remains challenging because *Bartonella spp.* are fastidious organisms and conventional culture has a low diagnostic yield [1,9,10].

Serological assays detecting IgM and IgG antibodies against *B. henselae* are widely used but are influenced by factors such as the timing of sample collection, patient immune status, and cross-reactivity with other pathogens [9–11]. Targeted PCR and metagenomic next-generation sequencing (mNGS) provide rapid and sensitive molecular methods for the direct detection of *B. henselae* DNA from clinical specimens and are particularly useful for culture-negative or atypical infections [12,13].

Musculoskeletal involvement in CSD, including osteomyelitis and arthritis, represents an uncommon manifestation and has only rarely been reported in the literature [4,6]. In this case, we report a young immunocompetent female who developed persistent knee joint swelling following a cat scratch. During her treatment at Peking University People's Hospital, conventional microbiological tests were negative. However, the diagnosis of *B. henselae* infection was confirmed through a combination of mNGS, quantitative PCR (qPCR), and the patient's exposure history. This case extends the clinical spectrum of CSD by

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illustrating prosthesis-associated localized joint infection due to *B. henselae* in an immunocompetent adult and underscores the diagnostic value of mNGS in culture-negative bone and joint infections.

Case

On June 17, 2024, a 28-year-old female presented to the outpatient clinic at our hospital with a five-month history of progressive swelling of the right knee. The patient underwent distal femoral tumor resection and prosthetic replacement for osteosarcoma in January 2011. In March 2016, she was treated at our hospital for a prosthetic infection and successfully underwent revision surgery. After the revision, she remained clinically stable until approximately five months before the current presentation, when swelling of the right knee gradually developed without any obvious precipitating factors.

The patient's outpatient blood tests showed the following elevated values: erythrocyte sedimentation rate (39 mm/h; reference range 0–20 mm/h), total protein (86.7 g/L; reference range 65–85 g/L), urea (7.9 mmol/L; reference range 2.8–7.2 mmol/L), and uric acid (412 μmol/L; reference range 155–357 μmol/L). Color Doppler ultrasound of the right knee revealed a solid-cystic mass (120 × 99 × 95 mm) anteromedially with clear boundaries, predominantly anechoic areas, irregular echoes, and free margins, suggesting proliferative synovial tissue. Enhanced CT showed a low-density lesion (8.8 × 5.7 cm) medial to the prosthesis, while a bone scan indicated increased perfusion and metabolism around the prosthesis and medial knee, raising suspicion of infection. Therefore, based on the patient's medical history and auxiliary test results, she was admitted for further treatment.

On admission, the physical examination revealed normal temperature, pulse, respiration, and blood pressure. The patient's routine blood tests showed an increase in white blood cell count ($12.25*10^9$/L; reference range 3.5–9.5$*10^9$/L), neutrophil count ($8.74*10^9$/L; reference range 1.8–6.3$*10^9$/L), and plateletcrit (0.31 %; reference range 0.11–0.27 %). On the third day after admission, under general anesthesia, the patient underwent excision of the knee joint mass and debridement of necrotic skin and subcutaneous tissue.

During surgery, a medial parapatellar approach was used. Approximately 50 mL of blood-tinged joint effusion was aspirated with a syringe and sent for microbiological culture and mNGS. Several cystic and soft tissue masses around the medial side of the knee were excised, and representative specimens were submitted for pathological examination and microbiological culture. All specimens were placed in sterile containers without preservatives and promptly transported to the microbiology laboratory. The joint effusion was completely evacuated, the cyst walls and nonviable soft tissues were thoroughly debrided, and a drainage tube was left in place. Postoperatively, the wound was irrigated routinely, and the patient received symptomatic and supportive care.

The bacterial cultures of the joint effusion and drainage fluid obtained during surgery were negative. Aerobic and anaerobic bacterial cultures were performed on standard media and incubated for up to 5 days before the results were reported as negative. Additionally, mNGS of the joint effusion identified *B. henselae*. Library preparation, sequencing, and bioinformatic analysis were performed as previously reported [14]. In this sample, 27 specific sequence reads were detected, corresponding to 0.1 % genome coverage and a 1992-bp coverage length using GCF_019930925.1 as the reference genome. The RPM ratio was 1.9, exceeding the predefined cutoff of 1.0 in our pipeline and therefore interpreted as positive (Fig. 1). To verify the mNGS results, a qPCR assay targeting a fragment of the *B. henselae* NADH ubiquinone oxidoreductase subunit G (*nuoG*) gene was performed according to a previously published report [3]. The assay utilized the primers F-Bart (5′-CAATCTT CTTTTGCTTCACC-3′) and R-Bart (5′-TCAGGGCTTTATGTGAATAC-3′), along with the hydrolysis probe FAM-5′-TTYGTCATTTGAACACG-3′ [BHQ1]-3', where Y denotes C or T according to the IUPAC nucleotide code. The qPCR result was positive. Upon further inquiry into the patient's history, it was revealed that she had sustained a scratch on the forearm from a cat approximately one month before the onset of knee swelling. After consultation with the Infectious Diseases Department, the patient was diagnosed with CSD caused by *B. henselae*.

After the surgery, the patient's condition remained stable, and recovery was progressing well. She was discharged on the 8th day of hospitalization. Discharge instructions included oral minocycline and rifampin for continued anti-infective therapy. The prescribed regimen was minocycline 100 mg every 12 h (total daily dose 200 mg) and rifampin 300 mg every 12 h (total daily dose 600 mg) for a duration of 8 weeks. Liver and renal function tests were monitored during therapy, and no significant adverse effects were observed. The case's clinical history timeline is shown in Fig. 2.

Follow-up after discharge showed that, after 8 weeks of oral antibiotics, the patient's knee joint swelling had resolved (Fig. 3). However, she still experienced some mild daytime edema in the lower leg without significant functional limitation. Hematological tests performed at an outside facility showed mildly elevated erythrocyte sedimentation rate (26 mm/h; reference range 2–25.7 mm/h) and high-sensitivity C-reactive protein (6.1 mg/L; reference range 0–6 mg/L), suggesting partial improvement but not full normalization. No repeat CT or MRI was performed after discharge; follow-up was based on clinical assessment and laboratory markers.

Discussion

Bartonella species are small, non-capsulated pleomorphic gram-negative rods with fastidious growth requirements. The culture process requires enriched media, a CO_2-enriched atmosphere, and prolonged incubation, often up to 45 days before visible colonies appear. These demanding conditions substantially limit both the sensitivity and the practicality of routine culture for *Bartonella* infections and may explain why *B. henselae* was not detected in the standard cultures of joint

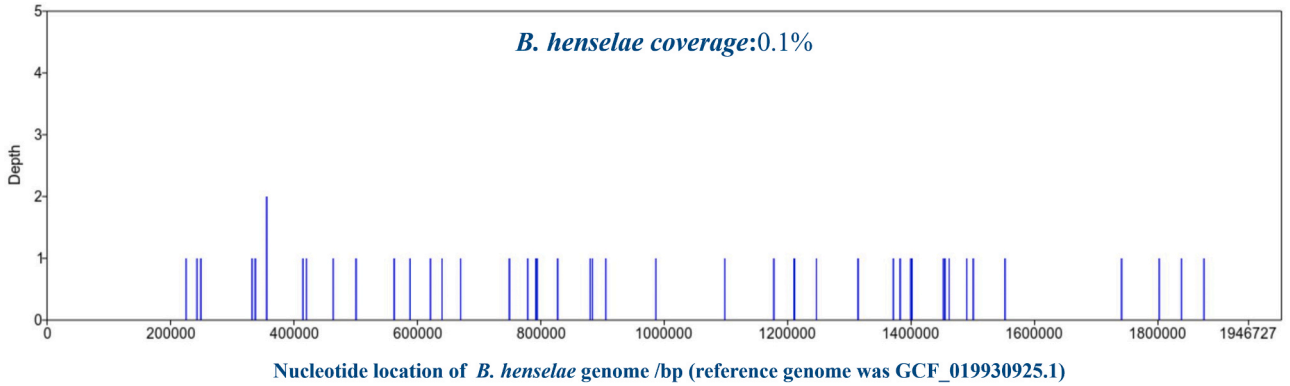

Fig. 1. Metagenomic next-generation sequencing (mNGS) coverage of the patient's joint effusion reads mapped to the *B. henselae* genome.

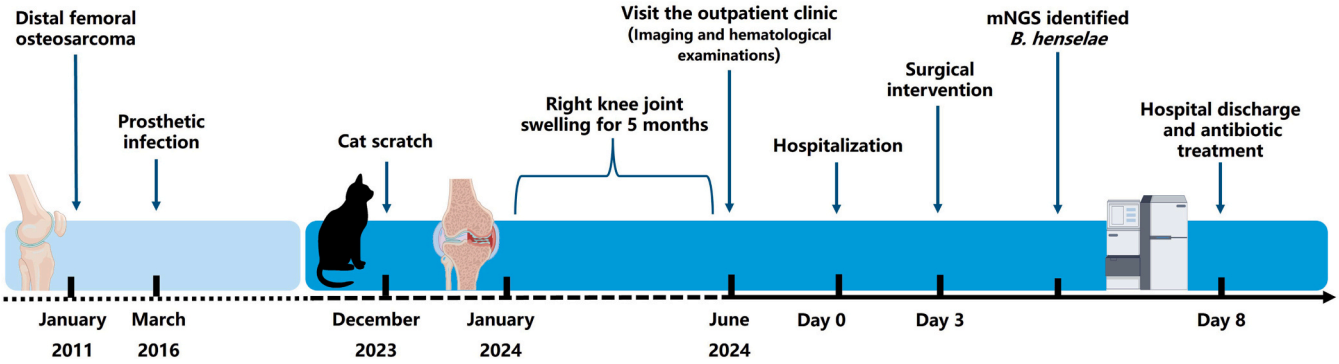

Fig. 2. Timeline of the clinical course of this case.

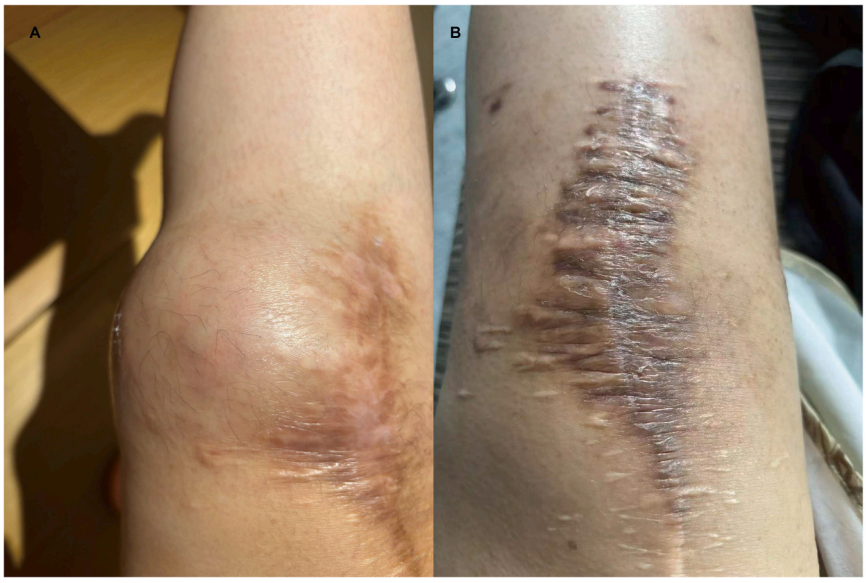

Fig. 3. The patient's right knee joint. (A) Prior to surgery. (B) Eight weeks after surgery and oral antibiotic therapy.

effusion and drainage fluid in this case [1].

Serological methods detecting IgM and IgG antibodies to *B. henselae* are widely used for laboratory diagnosis. However, their performance is affected by immune status, the timing of specimen collection, and potential cross-reactivity with other pathogens, all of which can influence test sensitivity and specificity [9–11]. In our patient, *Bartonella* serology was not performed because *B. henselae* infection was not initially suspected, and once the pathogen had been identified by mNGS and confirmed by qPCR, additional serological testing was not considered necessary for diagnosis.

Molecular techniques, including targeted PCR and mNGS, offer rapid, sensitive, and specific approaches for the direct detection of *Bartonella* DNA from clinical samples. The analysis of microbial nucleic acid sequences in clinical samples through mNGS allows comparison with curated database sequences to identify potential pathogens. This hypothesis-free strategy is particularly valuable in diagnosing culture-negative, atypical, or complex infections [12,13]. In this case, *B. henselae* was detected through mNGS of joint effusion, with 27 specific sequence reads, 0.1 % genome coverage and an RPM ratio of 1.9, and these findings were further corroborated by a positive qPCR targeting the *nuoG* gene. Taken together, the mNGS and qPCR results strongly support a true infection rather than environmental or laboratory contamination.

Human infection with *B. henselae* typically presents as CSD, characterized by lymphadenopathy, fever, headache, and skin lesions at the site of the cat scratch [6]. In some patients, *B. henselae* can cause chronic bacteremia, infective endocarditis, osteomyelitis, neuroretinitis, bacillary angiomatosis or peliosis, thrombocytopenia, and other complications [4,6,7]. In our patient, the chief complaint was knee joint swelling in the absence of typical systemic manifestations such as fever or lymphadenopathy. Only after *B. henselae* was identified by mNGS did further history taking reveal a cat scratch approximately one month prior to symptom onset, which prompted the diagnosis of CSD. The patient's clinical presentation did not align with the typical description of CSD and initially mimicked prosthetic joint infection or localized osteomyelitis caused by more common bacteria. Prior to this case, only one review of *B. henselae* had mentioned its potential to cause arthritis [4]. This finding highlights the diversity and non-specificity of the clinical manifestations of CSD and underscores the importance of considering *Bartonella* infection in the differential diagnosis of culture-negative bone and joint infections.

In immunocompetent individuals, uncomplicated CSD is usually a self-limited disease that resolves spontaneously or with minimal therapy [6,15]. However, atypical or complicated forms, such as endocarditis, osteomyelitis, and prosthesis-associated joint infection, may require prolonged antimicrobial treatment and sometimes surgical intervention [4,7]. Our patient was immunocompetent but developed a severe localized joint infection requiring surgical debridement and extended antibiotic therapy, suggesting that host immune status alone does not fully predict disease severity.

In this case, conventional bacterial cultures of joint effusion and drainage fluid were negative despite clinical and imaging findings strongly suggestive of infection. Common causative agents of prosthetic joint infection, such as *Staphylococcus aureus*, *streptococci* and *Cutibacterium acnes*, were considered less likely because repeated culture results remained negative. The temporal association with a cat scratch approximately one month before symptom onset, combined with mNGS detection and qPCR confirmation of *B. henselae* from joint effusion, narrowed the differential diagnosis and supported a final diagnosis of CSD with bone and joint involvement. Therefore, this case illustrates the diagnostic value of mNGS for fastidious, slow-growing, or viable-but-nonculturable organisms in culture-negative prosthetic joint or osteoarticular infections.

Conclusion

This case illustrates a rare presentation of CSD caused by *B. henselae*, manifesting as bone and joint infection in an immunocompetent adult with a history of prosthetic joint surgery. The patient's atypical clinical symptoms (isolated knee swelling without fever or lymphadenopathy) and negative results of conventional microbiological tests underscore the complexity and challenges of diagnosing CSD. When evaluating culture-negative prosthetic joint or osteoarticular infections, especially in patients with a history of cat scratch or other animal exposure, clinicians and microbiologists should consider *B. henselae* and other fastidious organisms in the differential diagnosis. Precise pathogen identification was achieved through mNGS of joint effusion, which facilitated rapid diagnosis and informed targeted antimicrobial therapy. These findings highlight the potential involvement of *B. henselae* in complex and atypical infections and underscore the diagnostic value of mNGS as a complementary tool to conventional methods in culture-negative infections.

Author statement

All authors approved the final version, confirm originality and no conflict of interest, and consent to submission. Patient consent was obtained and data is available on request.

CRediT authorship contribution statement

Yuyao Yin: Methodology, Formal analysis, Data curation. **Xingyu Wu:** Writing – original draft, Methodology, Formal analysis, Data curation. **Lingxiao Sun:** Methodology, Formal analysis, Data curation. **Yifan Guo:** Methodology, Formal analysis, Data curation. **Tao Ji:** Methodology, Formal analysis, Data curation. **Qianyu Shi:** Methodology, Formal analysis, Data curation. **Hui Wang:** Writing – review & editing, Supervision, Resources, Project administration, Conceptualization.

Consent

Informed consent was obtained from the patient for publication of this case report and any accompanying images.

Ethical approval

Not applicable. Written informed consent was obtained from the patient for publication of this case report and accompanying images.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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None to declare.

Data availability

Not applicable.

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