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CASE REPORT

Brucellar Knee Arthritis with Knee Joint Tuberculosis: A Case Report and Review of the Literature

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Abstract: *Brucella* and *Mycobacterium tuberculosis* (MTB) primarily affect the spine and only rarely the knee joint in osteoarticular disease in adults. We present an unusual instance of brucellar knee arthritis combined with knee joint tuberculosis. A 59-year-old man was initially diagnosed with brucellar knee arthritis in the orthopedics department of our hospital, while two weeks of standardized treatment did not improve the joint discomfort and inflammation indexes. Subsequent evaluation of serum tuberculosis interferon-gamma release assays (TB-IGRAs) and the effectiveness of empirical anti-tuberculosis therapy confirmed the mixed infection of tuberculosis. This case report demonstrates that clinical signs and imaging for brucellar knee arthritis and knee joint tuberculosis are similar. Patients with both disorders are more likely to be misdiagnosed or have their diagnosis delayed; clinicians should be aware of this uncommon combination of mixed infections.

Keywords: brucellar knee arthritis, knee joint tuberculosis, mixed infections, case report

Introduction

Brucellosis is endemic to Australia, India, the Mediterranean region, and northern China, a zoonosis transmitted predominantly by sheep and through cattle and pigs.[1] As an intracellular parasite, Brucella is ingested by phagocytes and reproduces continuously after entering the organism; when the human immunity is low, the bacteria can be released into the bloodstream and cause brucellosis.[1] Patients with brucellosis have a rate of osteoarticular system involvement ranging from 10% to 85%, and the spine is usually infected with infection of the knee joint unusual in adults.[2] Globally, tuberculosis is the leading cause of health problem, particularly in developing countries; inflammation, bacterial toxicity, immune damage, and bacterial proliferation are possible causes of tuberculosis caused by MTB.[3] MTB causes tuberculosis, which primarily affects the respiratory system; extrapulmonary tuberculosis is less common; again, the spine is the most prevalent location for osteoarticular tuberculosis in adults, followed by the knee joint.[4] Here, we present an unusual adult case of concomitant brucellar and tubercular knee joint septic arthritis.

Case Presentation

A 59-year-old male patient presented to the orthopaedic department of our institution with a 5-month history of left-knee pain and more recent activity restrictions for 10 days. This patient, an electrician, had worked around the sheepfold 10 months before, developing transient fever and fatigue with subsequent symptoms improvement after taking anti-inflammatory medication. The patient then developed knee pain, which worsened progressively. Serum agglutination test (SAT) was positive (1:160) in the local hospital, and he was transferred to our institution for further treatment.

The patient's core temperature was 38.3°C on admission. Physical examination showed a left knee joint that was obviously swollen with a positive floating patella test, active flexion and extension of left-knee joint were limited. Blood parameters revealed white blood count (WBC) 8.47×109/L with lymphocytosis, erythrocyte sedimentation rate (ESR) 72 mm/hr and C-reactive protein (CRP) 66.2 mg/L. The biochemical tests were all normal. Immunological tests showed

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that Rose Bengal Plate Agglutination Test (RBPT) and SAT (1:200) were positive and serum anti-tuberculosis antibody test was negative. X-ray film of the left-knee joint showed patchy osteopaenia of the distal femur and proximal tibia without obvious joint space narrowing (Figure 1A and B). Magnetic resonance imaging (MRI) showed associated bone marrow with diffuse patchy abnormal signal on T2-weighted imaging (T2WI), local full-thickness defect of patellar cartilage and knee joint synovitis (Figure 1C–E). X-ray and computerized tomography (CT) of the chest showed no evidence of pulmonary involvement or enlarged mediastinal lymph nodes. A presumed diagnosis of brucellar knee arthritis was made. The left knee joint underwent arthrotomy, sampling of discoloured joint fluid and irrigation. Aspirate was culture-negative; however, *Brucella melitensis* (*B. melitensis*) was detected by real-time polymerase chain reaction (Figure 2). HE staining of knee joint effusion and inflammatory tissue revealed inflammatory cell infiltration, while acid-fast staining was negative (Figure 3A and B). Combination therapy with rifampicin (0.6 g po qd; Guangdong Hengjian Pharmaceuticals), doxycycline (0.1 g po bid; Jiangsu Lianhuan Pharmaceuticals) and cefotaxime-sulbactam (2.25 g ivgtt q8h; Xiangbei Weierman Pharmaceuticals) were administered post-operatively.

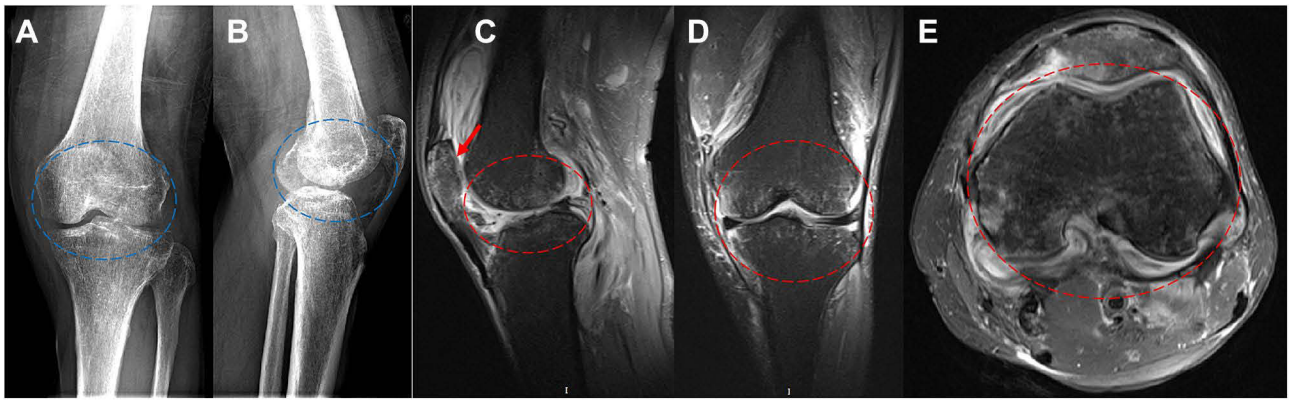

Figure 1 On admission to the hospital, X-ray and MRI images were taken of the left knee joint. (**A** and **B**) An X-ray of the distal femur and the proximal tibia revealed patches of osteopenia (blue circle). (**C–E**) There was a synovial infection in the knee joint, a localized full-thickness defect in the patellar cartilage (red arrow), and a diffuse patchy signal in the bone marrow on T2-weighted imaging (red circle).

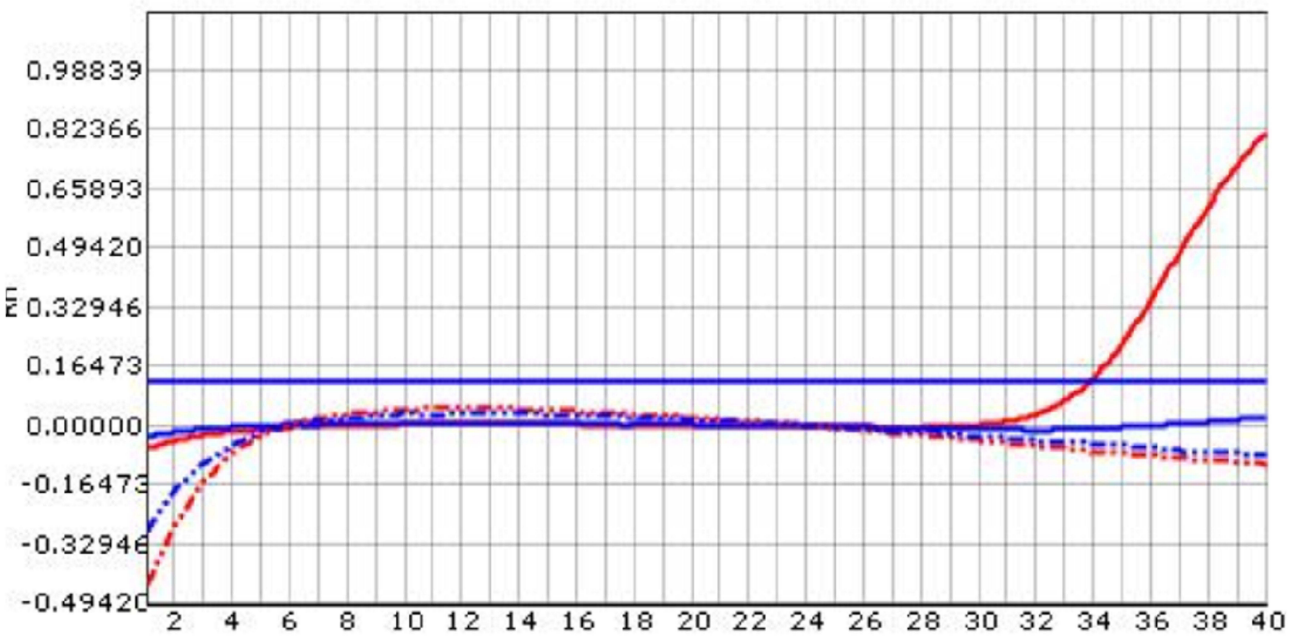

Figure 2 *Brucella melitensis* was detected by real-time PCR, real-time PCR showed that the DNA content of *Brucella melitensis* (Solid red line) increased in 32 cycles.

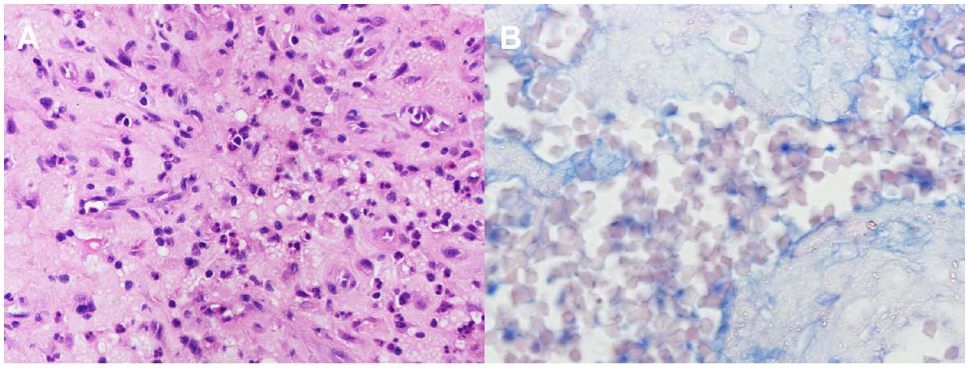

Figure 3 Pathological staining of knee joint effusion and inflammatory tissue. (**A**) Inflammatory cell infiltration was seen by HE staining. (**B**) Acid-fast staining was negative.

Left knee joint symptoms did not improve after two weeks of anti-brucellosis treatment. Inflammatory indexes did not diminish significantly (ESR 68mm/hr, CRP 66.1mg/L). Subsequently, knee joint tuberculosis was considered when serum TB-IGRAs were positive. Empirical anti-tuberculosis medications with isoniazid (0.3 g po qd; Shenyang Hongqi Pharmaceuticals), ethambutol (1 g po qd; Guangzhou Baiyunshan Pharmaceuticals) and pyrazinamide (0.5 g po tid; Chongqing Huabang Pharmaceuticals) were added.

Within three days, the pain in the left knee improved, CRP fell to 29.40 mg/L and ESR to 60mm/hr. Symptoms continued to settle and the patient was discharged from hospital 10 days later. Anti-brucellosis therapy was maintained for 5 months after discharge: rifampicin (0.6 g po qd; Guangdong Hengjian Pharmaceuticals) and doxycycline (0.1 g po bid; Jiangsu Lianhuan Pharmaceuticals). Anti-tuberculosis therapy was maintained for 9 months in all: 3-month intensive therapy and 6-month consolidation therapy), 3-month intensive therapy includes rifampicin (0.6 g po qd; Guangdong Hengjian Pharmaceuticals), isoniazid (0.3 g po qd; Shenyang Hongqi Pharmaceuticals), ethambutol (1 g po qd; Guangzhou Baiyunshan Pharmaceuticals), pyrazinamide (0.5 g po tid; Chongqing Huabang Pharmaceuticals) and 6-month consolidation therapy includes rifampicin (0.6 g po qd; Guangdong Hengjian Pharmaceuticals), isoniazid (0.3 g po qd; Shenyang Hongqi Pharmaceuticals). Symptoms were completely resolved and inflammatory indexes were normal at the end of treatment.

At last follow-up five years later, the patient had no discomforts in the left knee. X-ray showed resolution of previous abnormal X-ray appearances of the distal femur and proximal tibia (Figure 4A and B). MRI changes were also largely resolved (Figure 4C–E). Blood tests showed WBC of 6.28×10^9/L with no lymphocytosis, CRP 3.9mg/L, ESR 7mm/hr. The results of all the biochemical tests were normal. Immunological tests including serum anti-tuberculosis antibody, TB-IGRA, RBPT and SAT were all negative.

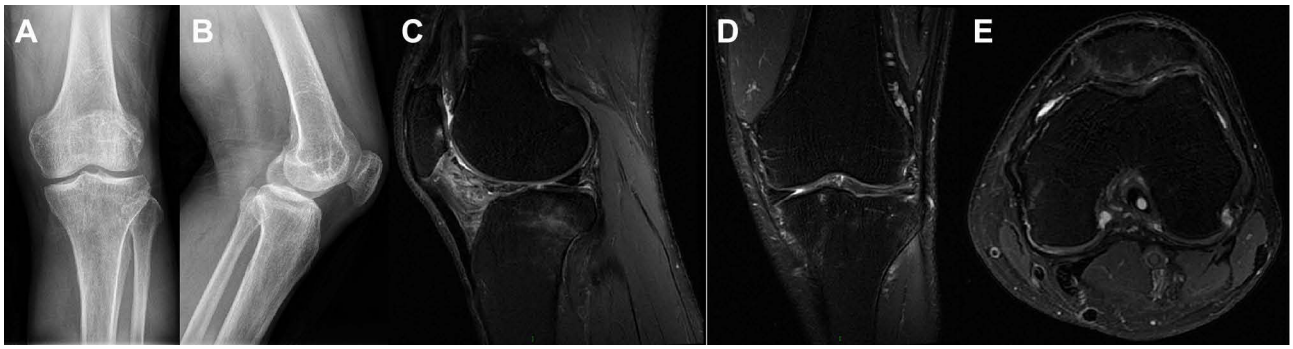

Figure 4 After five years, X-rays and MRI scans of the left knee joint were taken. (**A** and **B**) The X-rays showed that the distal femur and proximal tibia had resolved from the previous abnormal X-ray appearances. (**C–E**) It was also noted that the MRI changes were largely resolved.

Discussion

Concomitant infection with *Brucella* and MTB has only been recorded in one instance: a patient with brucellar spondylitis and spinal tuberculosis;[5] however, no case of brucellosis with tuberculosis of the knee joint has been described. There are only four cases of mixed infections of knee joint tuberculosis to date (Table 1). Most cases of *Brucella* infection are caused by skin and mucous membrane injury followed by the consumption of contaminated meat or dairy products; Brucella may also spread via the respiratory tract, blood transfusion, and placental transmission.[10–12] The patient in our report had no direct contact with a zoonotic source of infection and was presumably infected with *Brucella* via the respiratory system. The rarity of mixed infections, unusual infectious sites, and unusual transmission methods are features of this case.

Bacterial isolates from blood, bone marrow, synovial fluid, and other tissues are the gold standards in diagnosing brucellosis, but positive bacterial culture is challenging to achieve in chronic disease, so real-time polymerase chain reaction (real-time PCR) is the usual detection method.[13,14] The WBC count is often average or low, and lymphocyte count is increased in most patients; ESR is increased in the acute phase of the disease, yet is generally normal in the chronic phase.[15,16] Immunological tests such as RBPT and SAT have significant diagnostic value, SAT titer ≥1:160 is highly suggestive of *Brucella* infection.[13]

Rifampicin and doxycycline are the most often-utilized drugs in the acute phase of brucellosis, whereas rifampicin, doxycycline, and fluoroquinolones/third-generation cephalosporins are more commonly used in chronic or refractory infections.[17,18] It is possible to lower the risk of recurrence by continuing the course of medication beyond three months in patients with bone and joint system involvement.[19] During the 5-year follow-up period, no recurrence of the infection was seen in our patient treated with a triple regimen of rifampicin, doxycycline, and cefotaxime-sulbactam for half a year.

Research on extrapulmonary tuberculosis is mostly reported in developed countries, with fewer studies conducted in developing and undeveloped nations.[20,21] Recent studies indicate that extrapulmonary tuberculosis may be rising in China, a phenomenon that should be noted by physicians treating infectious diseases.[4,22,23]

The local symptoms (pain, swelling, joint dysfunction) and systemic symptoms (fever, fatigue, hyperhidrosis) in patients with osteoarticular tuberculosis are similar to those of brucellosis when the osteoarticular system is involved, and

Table 1 Literature Review of Knee Joint Tuberculosis with Mixed Infections

Author	Infection Type	Clinical Characteristics	Method of Diagnosis	Treatment Regimen	Clinical Outcomes
Kumar et al (2016)[6]	*Aspergillus* and *tuberculosis*	Irregular fever and increasing pain in right hip and knee	Bacterial culture, acid fast bacilli culture, fungal culture, TB polymerase chain reaction, synoviumbiopsy	Debridement, intravenous voriconazole, and antitubercular drugs	Well
Kuner et al (2019)[7]	*Mycobacterium bovis* and *Candida guilliermondii*	Persistent swelling of the knee and persistent wound scab	Bacterial culture, scintigraphy, tissue sampling and sonication of all implant parts	Tuberculostatic and mycocide medication, a two-stage revision knee arthroplasty	Well
Opara et al (2007)[8]	*Staphylococcus aureus* and *tuberculosis*	Pain in the left knee, fever and swelling in the popliteal fossa; worsening pain, swelling, and stiffness of left knee	Bacterial culture, acid-fast bacilli culture, synovialbiopsies	Incision and drainage of the popliteal swelling, arthroscopic lavage, splintage and flucloxacillin with fusidic acid, anti-tuberculous quadruple therapy	Persistent destructive changes in the joint
Remalante-Rayco et al (2021)[9]	*Mycobacterium tuberculosis, Pseudomonas aeruginosa, Acinetobacter baumannii*	Right knee swelling with fungating masses and white-yellow discharge	Acid-fast bacillus smear, *Mycobacterium tuberculosis* PCR test, aerobic culture, and histopathology	Antibiotic therapy, debridement, partial synovectomy, arthrotomy, and a flap coverage with split-thickness skin graft	Well

there are no specific differences in imaging findings; thus, misdiagnosis or delayed diagnosis is common.[5] TB-IGRA is represented by T-SPOT. TB assay (T-SPOT) and GeneXpert MTB/RIF (Xpert) have a higher detective efficiency for extrapulmonary tuberculosis, T-SPOT has higher sensitivity, and Xpert has higher specificity. However, T-SPOT cannot distinguish between active tuberculosis, latent infection, and previous infection, the World Health Organisation (WHO) recommends the application of Xpert in the diagnosis of extrapulmonary tuberculosis.[24,25] The accuracy of Xpert and T-SPOT in early diagnosis of osteoarticular tuberculosis is higher than other tests, such as serum anti-tuberculosis antibody test.[26,27] A negative result of serum anti-tuberculosis antibody test led to an early missed diagnosis of knee joint tuberculosis in this case. Two weeks of anti-brucellosis medications did not relieve knee joint symptoms, and only a positive T-SPOT, a negative chest CT, and the effectiveness of empirical anti-tuberculosis therapy confirmed left-knee joint tuberculosis. A high index of suspicion, in conjunction with wide-ranging diagnostic methods, should be combined to reduce the occurrence of misdiagnosis and delayed diagnosis in practical work.

The chemotherapy regimen for bone and joint tuberculosis is divided into short-term chemotherapy (6 months) and long-term chemotherapy (≥9 months). There is no consensus on the time required for chemotherapy in bone and joint tuberculosis patients due to the lack of large-scale and multicenter studies in developing countries. However, most centers continue to use long-term chemotherapy regimens.[28,29] Aryal et al[29] compared the efficacy of short-term treatment and long-term treatment in patients with spinal tuberculosis; the results showed no significant difference in curative rates of relapse between the two regimens. In this article, the patient was treated with a 9-month chemotherapy regimen: 3-month intensive therapy (isoniazid, rifampicin, pyrazinamide, ethambutol) and 6-month consolidation therapy (isoniazid, rifampicin). There were no adverse drug reactions during chemotherapy and no recurrence during follow-up for five years.

Extrapulmonary tuberculosis tests have a high false-negative rate.[30] Even if tuberculosis-related tests are negative, knee joint tuberculosis should be considered if long-term anti-brucellosis medications are ineffective in individuals with brucellar knee arthritis. Brucellar knee arthritis and knee joint tuberculosis overlap in the use of rifampicin treatment, but the use of an anti-brucellar regime cannot achieve a cure for tuberculosis.[17,29] Delayed diagnosis and treatment will not arrest the progression of knee joint tuberculosis.

Conclusion

In conclusion, brucellar knee arthritis with knee joint tuberculosis is unusual in clinical practice. The symptoms, signs, and imaging examinations of these two diseases are very similar. Clinicians should be aware of the potential for this uncommon combination of infections so that they can avoid misdiagnosis or delayed diagnosis.

Statement

The patient provided informed consent for publication of the case. No ethics committee approval was required for this study as the data had been analyzed in a retrospective manner.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors have no conflicts of interest to declare in this work.

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