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A case of drug fever in the treatment of *Brucella* arthritis in a child: a case report

Shufang Pan[1], Zulipiya Moming[2], Maimaitiaili Tuerxun[2], Yutian Chong[1*] and Jianyun Zhu[1*]

Abstract

Brucellosis, a zoonotic ailment induced by the *Brucella* and some patients may present with joint involvement. This report describes a pediatric patient diagnosed with *Brucella* arthritis, presenting with swelling and pain in the right knee. The patient had a reoccurrence of fever due to sulfamethoxazole-trimethoprim allergy during treatment. Symptoms improved after adjusting the antimicrobial regimen to ceftriaxone and rifampicin. This case emphasizes the importance of the need for brucellosis as a differential diagnosis for arthralgia and fever in brucellosis- endemic areas. Furthermore, it emphasizes the importance of timely recognition that recurrent fever after effective anti-infective therapy must be considered as a possibility of drug fever.

Keywords *Brucella* arthritis, Child, Drug fever, Sulfamethoxazole-trimethoprim

Background

Brucellosis, a zoonotic infection transmitted to humans through the consumption of contaminated food products or contact with infected animals' tissues or bodily fluids, poses a significant public health concern [1, 2]. Musculoskeletal manifestations occur in a considerable proportion of patients, ranging from 10 to 85%. Among these, the sacroiliac joints (up to 80%) and spinal joints (up to 54%) are the most commonly affected sites [1]. In contrast, peripheral joint involvement is rare compared to spondylitis and spinal discitis [1]. It should be noted that brucellosis in pediatric patients deserves special attention, as the condition may easily evade detection in infants [3]. In children, the most prevalent osteoarticular manifestation is monoarthritis, often observed in the knee and hip joints [3].

For children younger than 8 years of age with brucellosis, sulfamethoxazole-trimethoprim (each tablet contains 400 mg of sulfamethoxazole and trimethoprim 80 mg, SMZ-TMP), rifampin, and gentamicin are recommended [4]. In this article, we report a case of *Brucella* arthritis with developed drug allergy following the use of SMZ-TMP. Poses a diagnostic and therapeutic challenge for clinicians.

Case presentation

A 4-year-old child initially sought medical attention at a local hospital clinic, where he underwent treatment comprising penicillin and acupuncture for persistent swelling and pain in his right knee. Unfortunately, his symptoms did not show substantial improvement. On 28 May 2022, he was subsequently referred to the Pediatrics clinic at our hospital for further evaluation.

Physical examination showed that the child was 97 cm tall and weighed 15 kg. There was no fever, but the right knee was markedly swollen with limited flexion and extension. The other system examination was

*Correspondence:
Yutian Chong
chongyt@mail.sysu.edu.cn
Jianyun Zhu
Zhujiany@mail.sysu.edu.cn
[1]Department of Infectious Diseases, The Third Affiliated Hospital of Sun Yat-sen University, 510630 Guangzhou, China
[2]Department of Infectious Diseases, The First People's Hospital of Kashi Prefecture, 844000 Kashi, China

unremarkable. Laboratory investigations revealed white blood cell(WBC) count −6.17×10^9/L, the high-sensitivity C-reactive protein (hsCRP) -15.51 mg/L, and procalcitoninogen (PCT)-0.116 ng/ml. As rheumatic arthritis was suggested by clinical presentation, we ran anti-streptococcal hemolysin O (ASO) at the time of admission but the result was negative. Considering other causes of arthritis, antinuclear antibody was performed, but the result came back negative as well. Because Kashi is an endemic area for brucellosis, brucella antibodies and blood cultures are routinely performed.

Abdominal ultrasound, cardiac ultrasonography, the spine (including cervical, thoracic, lumbar, and sacrococcygeal spine) and sacroiliac joints magnetic resonance imaging (MRI) did not reveal abnormalities. Serum *Brucella* IgG was positive and blood culture results were suggestive of *Brucella Malta* infection. Further investigation of the patient's medical history revealed consumption of unboiled camel milk two months prior, as well as a one-month history of intermittent fever preceding the onset of swelling and pain. Based on the clinical presentation and laboratory findings, a diagnosis of acute *Brucella* knee arthritis was established.

On June 5, we initiated treatment with proper antibiotics; PO SMZ-TMP (SMZ 25 mg/kg, TMP 5 mg/kg) q12h and PO rifampicin 15 mg/kg qd. The symptoms and signs receded gradually. On 12 June, the patient was discharged. The patient was instructed to continue using SMZ-TMP and rifampicin.

On June 14, the child experienced the onset of fever, reaching a maximum temperature of 40.0 °C, coupled with chills. Self-administration of ibuprofen reduces the temperature to normal, but the temperature continues to recur. On June 16, the child manifested scattered rashes on the cheeks, anterior chest, and anterior abdomen, accompanied by pruritus. When seeking medical attention at a local hospital, the patient received a prescription for ceftriaxone; however, symptoms did not exhibit improvement. Consequently, on June 18, the patient returned to our hospital for further treatment.

Upon physical examination, the child exhibited a blood pressure of 90/60 mmHg, a heart rate of 110 beats per minute and a respiratory rate of 14 breaths per minute. Complete blood count at admission revealed anemia(Hb: 101 g/L), leukopenia [WBC: 2.80×10^9/L, neutrophil (N) percentage 38.3%, eosinophil (EOS) percentage 9%], thrombocytopenia(PLT: 88×10^9/L). There is an absence of heterogeneous lymphocytes. Other laboratory investigations revealed, PCT increased to 8.66 ng/ml, and interleukin-6 (IL-6) reached 22.78 pg/ml. Liver function, renal function, and coagulation function tests demonstrate normal results. Influenza A virus ribonucleic acid (RNA), influenza B virus RNA, respiratory syncytial virus RNA, respiratory adenovirus RNA, Mycoplasma pneumoniae RNA, parainfluenza virus RNA, enterovirus universal RNA, and severe acute respiratory syndrome coronavirus 2 RNA tested negative. Cardiac ultrasound showed trace pericardial effusion and no vegetation. Chest and upper abdomen CT scans did not reveal abnormal findings. Given the clinical suspicion of uncontrolled infection, anti-infective programs were strengthened- addition ceftriaxone (2000 mg ivdrip qd). Additionally, we performed blood culture tests.

Blood cultures came back negative. Despite the treatment administered, the patient's temperature showed minimal improvement and an upward trend in EOS count raised suspicion of a potential allergic reaction to anti-brucella drugs. On 21 June, rifampicin and SMZ-TMP were discontinued. By June 22, the child's temperature returned to normal. On 25 June, the patient's temperature remained normal for three days, prompting the addition of rifampicin for antibrucella treatment. His body temperature stayed normal, so we thought the fever and rash were mainly due to SMZ-TMP allergy. Consequently, the anti-brucella treatment regimen was modified to incorporate rifampicin 15 mg/kg qd po and ceftriaxone 60 mg/kg qd ivdrip. Discharge was granted on June 28th.

Table 1 document the patient's condition during the hospitalization period, with notable changes in key parameters. The timeline reflects variations in WBC, N%, Hb, PLT, PCT, EOS, and IL-6 levels during the course of treatment and adjustments to medications. The data show the patient's response to treatment and the management of complications.

Following the patient's discharge, there were no observed clinical symptoms, and the patient adhered to the prescribed regimen of rifampin and ceftriaxone. The patient successfully completed the 6-week medication course.

Table 1 Laboratory test results

Date	WBC (×10^8/L)	*N*(%)	EOS (%)	Hb (g/L)	PLT (×10^8/L)	PCT (ng/ml)	IL-6 (pg/ml)
2022-05-28	6.17	36.2	2.2	119	223	0.116	N/A
2022-06-18	2.8	38.3	9.0	101	88	8.66	22.78
2022-06-21	2.28	27.3	15.0	100	87	4.26	8.4
2022-06-25	3.34	9.1	13.0	104	115	1.83	4.45

white blood cell count (WBC), neutrophil percentage (N%), eosinophil percentage (EOS%), hemoglobin (Hb), platelet count (PLT), procalcitonin (PCT), and interleukin-6 (IL-6), Not apply (N/A)

Discussion and conclusions

Monoarticular involvement in osteoarticular brucellosis is a prevalent clinical manifestation, particularly in pediatric cases. The frequency of this monoarticular pattern varies and has been reported in the range of 62–90% [5–7]. Furthermore, there is a consensus among authors that in this specific population, there is a distinctive predilection for the involvement of large joints located in the lower limbs. This observation underscores the importance of considering brucellosis as a possible differential diagnosis in pediatric patients with monoarticular arthritis, particularly in cases where large joints of the lower extremities are affected.

The initial presentation of knee swelling and pain, along with a preceding low-grade fever that spontaneously resolved, prompted the suspicion of rheumatic arthritis in the pediatric patient. Subsequent examination uncovered a negative serum ASO titer and demonstrated the ineffectiveness of penicillin treatment. A positive brucella-specific laboratory test and blood culture ultimately led to the diagnosis of brucellosis in the child.

Extensive literature emphasizes the variability and lack of characteristic features in the clinical presentation of brucellosis [8, 9]. Attaining a definitive diagnosis requires a meticulous history and epidemiological investigation. Consequently, clinicians should maintain a heightened suspicion of brucellosis when confronted with atypical symptoms, such as fever and joint pain, in individuals residing in an infected area. This case underscores the crucial significance of contemplating brucellosis in the field of differential diagnosis within an infected area, particularly when initial clinical features may mimic those of other rheumatic diseases.

Prompt diagnosis and treatment are essential to prevent complications and ensure a favorable prognosis for the patient. The patient's clinical course demonstrated the efficacy of rifampicin and SMZ-TMP in the treatment of brucellosis, as evidenced by the conversion of blood cultures and relief of knee pain. However, after 9 days of treatment the patient developed fever, followed by a rash and decreased complete blood count.

The recurrence of elevated temperature during anti-infective therapy should be considered not only for uncontrolled infections but also for the possibility of drug fever. In this case, the child demonstrated elevated temperature and inflammatory markers, but no significant pain in the right knee and elevated EOS, suggesting the possibility of drug allergy. Drug allergies can manifest as drug fever and drug rash.

The patient exhibited fever, a temperature exceeding 38.5 ℃, EOS% exceeding 10%, and negative results from differential diagnosis of blood cultures and hepatitis viruses. However, the absence of multiple enlarged lymph nodes, heterogeneous lymphocytes, a rash covering less than half of the body surface area, a disease duration of less than 15 days, among other factors, resulted in a DRESS scoring system score of 0. Consequently, the diagnosis of DRESS syndrome is not currently being considered.

Traditionally, the rate of relapse following treatment with conventional regimens has ranged from 5 to 15% [10]. In younger children (under 8 years of age), recommended medications include SMZ-TMP, rifampin, and gentamicin [11]. However, the combination of rifampicin and SMZ-TMP for a 6-week duration is considered the treatment of choice for brucellosis in this age group, with a relapse rate typically below 5% [12, 13]. Allergic reactions to SMZ-TMP, including anaphylactic shock in severe cases, have been reported [14, 15]. The demonstrated efficacy in this case aligns with its known effectiveness against *Brucella* [16].

This case emphasizes the importance of obtaining a detailed medical history, especially in populations in infected areas. In the course of treatment, in addition to observing the therapeutic effect, it is also necessary to pay attention to adverse drug reactions. If necessary, make timely changes to the treatment program to ensure that patients recover safely.

Abbreviations

SMZ-TMP	Sulfamethoxazole-trimethoprim
WBC	White blood cell
hsCRP	high-sensitivity C-reactive protein
PCT	procalcitonin
ASO	Anti-streptococcal hemolysin O
MRI	Magnetic resonance imaging
N%	Neutrophil percentage
EOS	Eosinophil
Hb	Hemoglobin
PLT	Platelet count
IL-6	Interleukin-6
N/A	Not apply

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Author contributions

S P and Z M wrote the main manuscript text and M T prepared Table 1. writing-review and editing: Y C and J Z.All authors reviewed the manuscript.

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Data availability

Not applicable (no datasets were generated or analyzed during the current study).

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

The patient provided written, informed consent for publication of the details of this case.

Competing interests
The authors declare no competing interests.

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