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Case Report

Brucellosis presenting as prolonged fever of unknown origin in a two-year-old child: a diagnostic challenge

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ABSTRACT

Brucellosis is a zoonotic disease with diverse clinical manifestations and is an uncommon but important cause of prolonged fever in children. Diagnosis may be delayed due to nonspecific symptoms, limited exposure history, and variable serologic findings. This report describes a two-year-old patient who experienced 17 days of recurrent fever associated with fatigue, myalgia, and diarrhea following a horse-related injury two months earlier. Extensive evaluation demonstrated elevated inflammatory markers, thrombocytosis, cervical lymphadenopathy, and hepatic lesions, but the etiology was unrevealing. A thorough exposure history prompted targeted zoonotic testing, which identified *Brucella*-positive IgM in the absence of detectable IgG, consistent with an acute *Brucella* infection in the appropriate clinical context. This case highlights the importance of detailed exposure history and consideration of brucellosis in the differential diagnosis of pediatric fever of unknown origin (FUO), even in the absence of classic presentation.

Keywords: Brucellosis, Pediatric fever of unknown origin, Zoonotic infection, Exposure history, Hepatic lesions, Prolonged fever

INTRODUCTION

Brucellosis is a chronic granulomatous infection caused by the *Brucella* species, which are gram-negative coccobacilli.[1] Brucellosis is the most prevalent bacterial zoonosis, with more than 2.1 million cases reported each year globally and poses significant risks to individuals involved in veterinary care, impacts national economies, and affects public health.[2] Humans acquire infection primarily through direct contact with infected animals or consumption of contaminated animal products, although transmission may also occur through environmental or occupational exposure.[1] In children, brucellosis may present with non-specific symptoms such as prolonged fever, malaise, and gastrointestinal complaints, which can delay diagnosis. FUO in pediatric patients poses a diagnostic challenge, requiring systematic evaluation for infectious, inflammatory, and malignant etiologies. This case demonstrates brucellosis as a rare but important cause of pediatric FUO and highlights the role of detailed history and targeted testing.

CASE REPORT

Patient presentation

A two-year-old child presented with prolonged fever for 17 days, with a maximum temperature of 103F (39.4 °C) associated with progressive fatigue, decreased activity, generalized body pain, reduced appetite, rhinorrhea, and intermittent watery diarrhea. There was no vomiting, rash, conjunctivitis, or mucocutaneous changes. No history of recent travel or known tuberculosis exposure was reported. The child lived in a household with five horses, two dogs, and two cats, and attended daycare. Approximately three to four weeks before presentation, the patient sustained a superficial scratch injury sustained while playing near a horse at a local farm.

Exposure history

The patient lives with 5 horses, 2 dogs, and 2 cats at home and attends daycare. There was no history of consumption of unpasteurized dairy products.

Medical history and examination

The patient was born full-term following an uncomplicated pregnancy and had no significant past medical history. Immunizations were up to date per CDC guidelines.

On admission, the patient appeared awake and alert but irritable and nontoxic. Physical examination revealed posterior pharyngeal erythema and cervical lymphadenopathy. No rash, hepatosplenomegaly, joint swelling, or neurological deficits were noted.

Investigations

Initial laboratory evaluation showed leukocytosis with reactive thrombocytosis and persistently elevated inflammatory markers. Blood, urine, and stool cultures remained negative. Viral testing, including respiratory viral PCR, Epstein-Barr virus serology, cytomegalovirus PCR, and enterovirus PCR, was negative.

Abdominal ultrasonography revealed a hypoechoic lesion in the right hepatic lobe near the inferior vena cava. Contrast-enhanced CT of the abdomen demonstrated a low-density hepatic lesion with two small peripherally enhancing foci. CT imaging also revealed multiple enlarged cervical lymph nodes. Echocardiography, bone scan, and MRI of the brain and lower extremities were unremarkable.

Infectious disease was consulted for further recommendations. A comprehensive evaluation for endemic fungal, parasitic, and zoonotic infections, such as *Bartonella*, *Brucella*, tularemia, leptospirosis, histoplasmosis, blastomycosis, and rheumatological conditions was undertaken.

Hospital course

Despite broad-spectrum empiric antibiotic therapy and supportive care, the patient continued to have daily febrile episodes during the initial hospitalization. Given the persistent fever, lymphadenopathy, elevated inflammatory markers, and hepatic lesions, incomplete Kawasaki disease was considered, and the patient received intravenous immunoglobulin and high-dose aspirin. Blood cultures remained negative after 48 hours, and empiric antibiotics were discontinued.

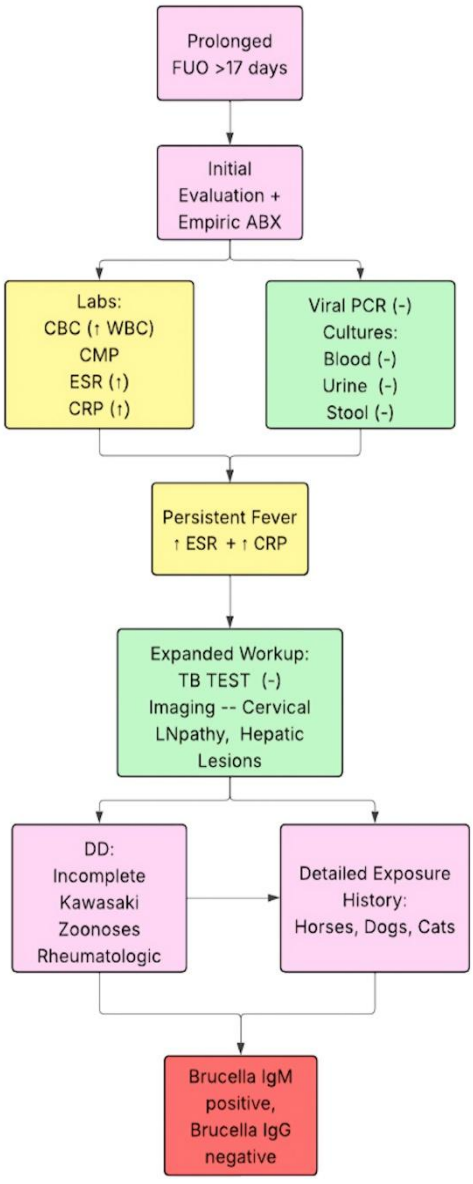

Figure 1: The stepwise diagnostic approach undertaken in this patient with prolonged fever of unknown origin.

*CBC=Complete blood count, WBC=White blood cell count, CMP=Comprehensive metabolic panel, ESR=Erythrocyte sedimentation rate, CRP=C-reactive protein, PCR=Polymerase chain reaction, TB=Tuberculosis, LNpathy=Lymphadenopathy, DD=Differential diagnostic and Ig=Immunoglobulin.

The patient was discharged in stable condition despite pending serological results. Subsequent confirmation of isolated *Brucella* IgM positivity, in conjunction with serological testing, revealed a *Brucella*-positive IgM, in conjunction with exposure history and clinical findings, supported the diagnosis of acute brucellosis. Appropriate antimicrobial therapy was initiated, and the case was reported to public health authorities. A summary of the diagnostic approach is depicted in Figure 1. This figure illustrates the stepwise diagnostic approach undertaken in this patient with prolonged FUO.

DISCUSSION

Brucella species infect a range of domestic and wild animals, and humans may acquire infection through contact with infected animals and their bodily fluids, including saliva, vaginal, and seminal secretions. Individuals living in rural areas or those who handle livestock, such as farmers and veterinarians, are at increased risk. Additional transmission routes include consumption of contaminated raw or unpasteurized dairy products, airborne exposure in slaughterhouses or meat-processing facilities, and, less commonly, laboratory exposure. Intrauterine transmission and rare cases via blood transfusion or bone marrow transplantation have also been reported.[3]

Twelve strains of *Brucella* spp. are known to infect humans, originating from six classical principal hosts: *B. melitensis* (sheep and goats), *B. suis* (pigs), *B. abortus* (cattle), *B. ovis* (sheep), *B. canis* (dogs), and *B. neotomae* (wood desert rats).[3] Among these, *B. melitensis*, *B. suis*, and *B. abortus* account for the majority of human brucellosis cases, with *B. melitensis* recognized as the most virulent.[4]

Brucella species are intracellular facultative pathogens that primarily infect macrophages and trophoblast cells. These organisms proliferate on mucosal epithelial surfaces and are subsequently internalized by mucosal macrophages and dendritic cells. This process enables *Brucella* bacteria to survive and replicate within phagocytic cells, evade immune responses, and disseminate to organs such as the reproductive tract, reticuloendothelial system, placental trophoblasts, and fetal lungs.[5] The incubation period of *Brucella* bacteria can range from five to six months. Upon ingestion, these bacteria reach lymphoid tissue via macrophages, multiply in the lymphatics, and spread to multiple organs, resulting in regional or systemic symptoms.[3]

Clinical presentation

Brucellosis most commonly presents with recurrent fever, sweating, arthralgia, and fatigue; however, symptoms can range from flu-like illness to more severe complications involving multiple organs.[3] Additional symptoms may include weakness, malaise, anorexia, myalgia, loss of appetite, vomiting, diarrhea, abdominal pain, and even miscarriages.[3-5] Depending on the duration of the disease, brucellosis may be categorized as acute (recovery within 6 months) or chronic (persistent symptoms for more than 6 months). Studies show patients with acute brucellosis tend to present with symptoms such as fever, arthritis, splenomegaly, diaphoresis, and lymphadenopathy.[6] Due to diverse clinical presentations, diagnosis can be challenging, resulting in misdiagnosis. If left untreated, it can progress to chronic brucellosis. Qureshi et al indicate that *Brucella* species attack the immune system of the host and cause a spectrum of symptoms ranging from fever, arthralgia, fatigue, to severe complications such as endocarditis and neurological disorders manifesting as chronic brucellosis.[3]

Some patients can present with non-specific abdominal pain and can have associated splenomegaly/hepatic lesions on imaging. Hematological abnormalities such as anemia, leukopenia, or thrombocytopenia may also occur. Studies also indicate that peripheral arthritis, hemorrhagic anemia, severe thrombocytopenia, and abdominal pain are more common presentations in pediatric patients than adults.[3]

Recurrent fevers in pediatric patients present a significant diagnostic challenge, requiring prompt and comprehensive evaluation to determine the underlying cause. In this case, a two-year-old patient presented with a persistent FUO for 17 days. Pediatric FUO is defined as a temperature exceeding 38.3°C at least once daily for more than eight days. Infections are the most common cause of pediatric FUO, followed by inflammatory conditions, neoplasms, and other etiologies, with some cases remaining undiagnosed.[7]

In this case, the patient exhibited non-pathognomonic symptoms, including fatigue, diarrhea, myalgia, arthralgia, lymphadenopathy, hepatic lesions, and elevated inflammatory markers such as CRP and ESR. These non-specific manifestations can be a manifestation of several inflammatory and infectious diseases. The multi-systemic nature of brucellosis complicates diagnosis and interpretation, earning it the designation of “a great imitator” due to its diverse presentations. The non-specific clinical manifestations of brucellosis require consideration of multiple differential diagnoses.

Table 1 summarizes diseases that seem similar to Brucellosis because of their similar symptoms but mentions how physicians can identify differences between them.

This case is notable for its atypical exposure history, as the patient did not have the commonly reported risk factor of unpasteurized dairy consumption. Instead, the primary animal exposure involved ownership of five horses, two dogs, and two cats. *Brucella* species are transmitted to humans primarily through direct contact with infected animals or ingestion of contaminated

animal products. Although horses are not primary reservoirs, indirect environmental exposure remains a potential route of transmission. Accurate diagnosis requires a thorough patient history, consideration of epidemiological factors, and multiple confirmatory laboratory tests.[14]

Table 1: Differential diagnoses of brucellosis highlighting conditions with overlapping clinical features and the key clinical, laboratory, and epidemiologic findings that aid in distinguishing them.

Conditions	Brucellosis mimicking signs/symptoms	Specific symptoms ruling out brucellosis
EBV	Fever, fatigue, abdominal pain, diarrhea, cervical lymphadenopathy	Exudative pharyngitis, lymphocytosis
Kawasaki disease	Patient's age elevated inflammatory markers lymphadenopathy	Absence of rash, bilateral nonexudative conjunctival injection, extremity changes red/swollen hands/feet), strawberry tongue
Bartonella	Animal exposure (horses/dogs/cats) hepatic lesions	Widespread lymphadenopathy, hepatosplenic micro-abscesses abscesses
Tularemia	Similar clinical presentation zoonotic exposure	No ulceroglandular disease associated with exposure to rodents/ rabbits/ ticks rather than livestock localized lesion rather than multi-systemic disease
***B. canis* infection**	Exposure to dogs	Human to human transmission; typically, through contact with infected canine secretions
Brucellosis	Fever, GI symptoms	Positive serology with exposure history

*Abbreviations: EBV=Epstein-Barr virus, GI=Gastrointestinal

As the symptoms can be chronic and persist for months to years as chronic brucellosis, primary care physicians need to obtain a thorough medical and dietary history when infection from contaminated food is suspected. Uncommon presentations and complications in adults can range from epidural abscess, septic arthritis, osteomyelitis, sacroiliitis, spondylodiscitis, hepatic abscess, spontaneous bacterial peritonitis, granulomas, ventriculoperitoneal shunt infection, epididymal-orchitis, and immune thrombocytopenic purpura. Rare cases can lead to Guillain-Barré syndrome, while death can be the result of complications such as endocarditis.[3]

In young children, brucellosis frequently presents with nonspecific symptoms such as prolonged fever and malaise, which can delay diagnosis. Limited ability to articulate symptoms and less apparent exposure histories further complicate early recognition.

Diagnosis

The diagnosis of acute brucellosis in this case was based on compatible clinical features, a relevant animal exposure history, imaging findings suggestive of systemic involvement, and positive *Brucella* IgM serology with negative IgG. Although blood cultures were negative, culture negativity does not exclude brucellosis due to low sensitivity and prolonged incubation requirements.

Isolated *Brucella* IgM positivity presents an interpretive challenge. One study found that among 17 patients with *Brucella* IgM-positive and IgG-negative serology and similar clinical presentations, none were ultimately diagnosed with brucellosis. Conversely, patients with both IgM and IgG positivity were confirmed to have the disease, underscoring the diagnostic complexity.[15] However, when interpreted in the appropriate clinical and epidemiologic context, IgM positivity may support the diagnosis of acute infection. In this case, extensive testing excluded alternative etiologies, and the clinical course was consistent with brucellosis.

Table 2: Serologic tests used in the diagnosis of brucellosis.

Tests	Target antibody	Diagnostic utility	Limitations
Rose Bengal test	IgM, IgG	Rapid screening test	False positives; low specificity
SAT	IgM, IgG	Commonly used confirmatory test	May be negative in early disease
ELISA-IgM	IgM	Detects acute infection	False positives possible
ELISA-IgG	IgG	Indicates past or chronic infection	May be negative early
Blood culture	Organism isolation	Gold standard	Low sensitivity; prolonged incubation
PCR (where available)	Bacterial DNA	Early diagnosis	Limited availability

*ELISA=enzyme-linked immunosorbent assay, Ig=Immunoglobulin, PCR=polymerase chain reaction, SAT=Standard agglutination test

Studies show that false-positive results may occur due to cross-reactivity with other gram-negative organisms such as *Yersinia enterocolitica*, *Escherichia coli* O157 and O116, *Francisella tularensis*, *Salmonella urbana*, *Vibrio cholerae*, *Xanthomonas maltophilia,* and *Afipia clevelandensis*.[16] In such scenarios, confirmation of brucellosis requires additional diagnostic modalities such as enzyme-linked immunosorbent assay (ELISA), serum agglutination test (SAT), and the Brucellacapt test. Table 2 summarizes the available serologic tests for the diagnosis of brucellosis, including their clinical utility and limitations.

Table 2 summarizes the key diagnostic and confirmatory tests for brucellosis.

Treatment

Treatment for brucellosis requires combination antimicrobial therapy with agents that can successfully penetrate macrophages' acidic intracellular environment to reduce relapse risk.[19] Treatment options for brucellosis are summarized in Figure 2.[19,20]

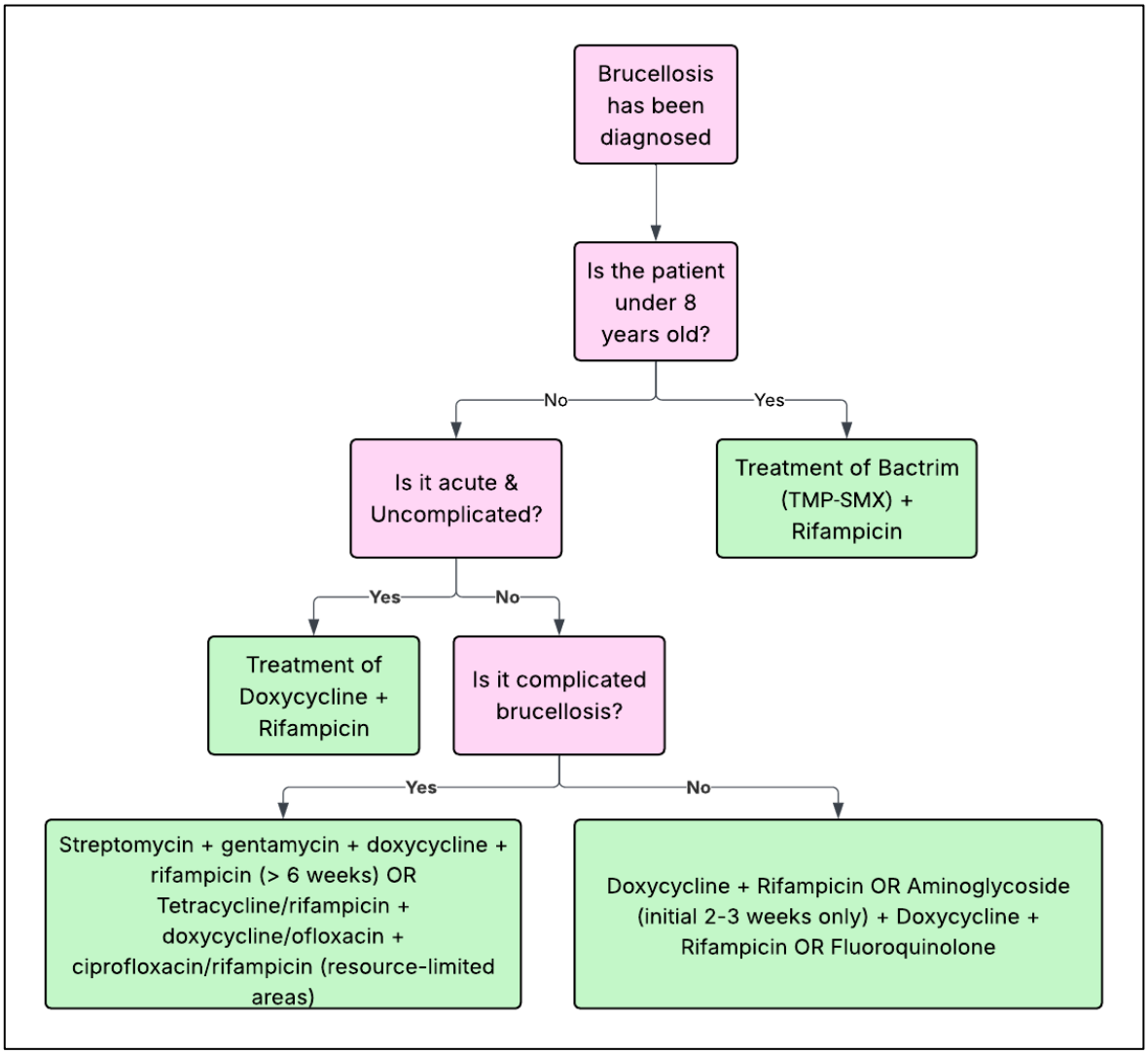

Figure 2: A treatment algorithm for brucellosis outlining initial and escalation treatments according to the patient's age and whether the disease is complicated or uncomplicated.

*Abbreviations: TMP-SMX=Trimethoprim-Sulfamethoxazole

Doxycycline and rifampicin are commonly used for treating acute and uncomplicated brucellosis and are expected to make a full recovery.[20] While fluoroquinolones are not routinely recommended as first-line therapy in pediatric patients, co-trimoxazole with an aminoglycoside such as gentamicin or rifampicin may be preferred in children.[19,20]

Additionally, patients need close monitoring and regular follow-ups with primary care physicians to increase the medication adherence. Antibiotic misuse may result in multidrug-resistant *Brucella* strains in endemic regions; hence, testing for brucellosis susceptibility is highly recommended to assess sensitivities and resistance to drugs using tests such as microdilution, E-tests, Kirby-

Bauer, and real-time PCR.[21] Brucellosis has a good prognosis with treatment, while incomplete treatment, non-compliance, and poor antibiotic selection can result in relapse (5-15%).[22]

Public health and brucellosis

The worldwide prevalence of human brucellosis has increased, with cases distributed across Europe, Asia, the Americas, and Africa. The highest incidence occurs in the Eastern Mediterranean region, particularly in countries such as Syria, Turkey, and Iraq. Other countries with elevated prevalence include Kyrgyzstan, Mongolia, Iran, Algeria, and Kenya.[3,14] Inadequate surveillance in these regions likely results in a significant underestimation of the disease burden, potentially leading to a 20 to 25 times higher prevalence rate. Control and management are particularly challenging in areas where livestock farming is the primary source of income, religious beliefs influence animal husbandry, and socioeconomic status is low. Effective interventions that protect these populations' safety without jeopardizing their livelihood remain to be developed and implemented.[14]

CONCLUSION

This case highlights the need for clinicians to employ a systematic diagnostic approach for managing pediatric FUO. Comprehensive exposure history, including direct and indirect contact with infectious agents, dietary practices, and epidemiological factors, is essential for identifying the causative agent and guiding appropriate treatment. Brucellosis should be considered in the differential diagnosis of prolonged FUO in pediatric patients, particularly when there is a history of animal exposure, even in the absence of classic risk factors. Early recognition and prompt initiation of appropriate antibiotics are critical to prevent complications and relapse.

Brucellosis is an important but often overlooked cause of pediatric fever of unknown origin. Isolated *Brucella* IgM positivity requires careful clinical correlation due to the potential for false-positive results. A detailed animal exposure history is critical in identifying zoonotic infections. Early targeted serologic testing can reduce diagnostic delay and unnecessary investigations. Multidisciplinary evaluation facilitates timely diagnosis, and appropriate management improves outcomes and reduces relapse risk.

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