Case Report

ANNALS OF MEDICINE & SURGERY

OPEN

Febrile neutropenia in an immunocompetent patient with brucellosis: a case report and literature review

Fasih Mand Khan, MBBS[a], Ariba Khan, MBBS[b], Sandesh Raja, MBBS[c], Adarsh Raja, MBBS[d], Asfia Qammar, MBBS[e], Aayush Chaulagain, MBBS[f,*]

Introduction and importance: Brucellosis is a zoonotic disease that can affect various organs, with symptoms like fever, lymphadenopathy, and arthritis. Hematologic complications, including febrile neutropenia, are rare. This report highlights the diagnostic and therapeutic challenges of brucellosis with febrile neutropenia.

Case presentation: A 36-year-old man presented with a 3-week history of fever, polyarthralgia, and night sweats. Examination showed febrile symptoms, joint swelling, and cervical lymphadenopathy. Laboratory tests revealed neutropenia and elevated inflammatory markers. Imaging was unremarkable, and blood cultures were negative, but brucellosis was confirmed by serology. Treatment with doxycycline and rifampicin led to clinical improvement.

Clinical discussion: Brucellosis diagnosis can be challenging due to nonspecific symptoms and requires high suspicion, especially in non-endemic areas. In this case, early identification and targeted therapy led to symptom resolution. This case underlines the importance of considering zoonotic diseases in febrile neutropenia with inconclusive initial findings.

Conclusion: Brucellosis with febrile neutropenia is rare but manageable with timely diagnosis and treatment, leading to favorable outcomes.

Keywords: brucellosis, case report, febrile neutropenia, serology, zoonotic disease

Introduction

Brucellosis is a zoonotic disease that is transmitted to humans through consumption of unpasteurized dairy products, direct contact with infected animal parts, or inhalation of infected aerosol particles[1,2]. Less than 10% of human brucellosis cases are clinically identified and reported[3]. In endemic regions, brucellosis is always included in the differential diagnoses for fever of unknown origin[4].

The most common symptoms of brucellosis are fever, fatigue, sweating, arthritis, hepatosplenomegaly, lymphadenopathy, and cytopenia. Neutropenia as a hematological manifestation of brucellosis is extremely uncommon[5]. Brucellosis diagnosis is confirmed based on clinical symptoms consistent with the disease, positive blood culture results, and/or a standard tube agglutination test showing a titer >1/160 upon admission for all patients[6,7]. Since brucellosis does not respond to the standard antibiotic treatment for febrile neutropenia, it can lead to treatment failure[8]. Brucellosis with febrile neutropenia is a rare combination to find in case reports. With a review of the clinical signs, test findings, and therapeutic strategy in this specific case, the goal of this case report is to document the infrequent occurrence of brucellosis with febrile neutropenia. This case report has been meticulously prepared in accordance with the SCARE 2023 guidelines[9].

Case presentation

A 36-year-old male with no prior medical history presented at a tertiary care hospital in New Jersey with a three-week history of fever and malaise. The patient described his fever as being cyclical, with peak temperatures in the late evening. He also reported associated profuse diaphoresis, decreased appetite, nonproductive cough, and pharyngitis. He denied recent travel history, sick contacts, exposure to animals, or consumption of uncooked meat. He was in a monogamous relationship. He denied both smoking history and illicit drug use and reported occasional alcohol consumption. He worked in a restaurant and handled raw meat.

On the initial examination, he was found to be febrile with a temperature of 39.6°C (103.3°F). He exhibited swelling and tenderness in both wrists and the proximal interphalangeal and distal interphalangeal joints of both hands, along with left-sided anterior cervical lymphadenopathy. Laboratory studies revealed the following: hemoglobin (Hb) 13.7 g/dL, mean corpuscular volume 85.2 fL, leukocyte count 1.40 × 10^3/μL, and platelet

[a]Fatima Memorial College of Medicine and Dentistry, Lahore, Pakistan, [b]Services Institute of Medical Sciences, Lahore, Pakistan, [c]Dow Medical College, Dow University of Health Sciences, Karachi, Pakistan, [d]Shaheed Mohtarma Benazir Bhutto Medical College Lyari, Karachi, Pakistan, [e]Baylor Scott & White Heart and Vascular Hospital, Dallas and [f]Department of Medicine, Patan Academy of Health Sciences, Patan, Nepal

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

*Corresponding author. Address: Department of Medicine, Patan Academy of Health Sciences, Lagankhel, Lalitpur 26500, Nepal.
E-mail: aayush.szmc@gmail.com (A. Chaulagain).

Annals of Medicine & Surgery (2025) 87:383–386

Received 24 July 2024; Accepted 24 November 2024

Published online 9 January 2025

http://dx.doi.org/10.1097/MS9.0000000000002823

count 204 × 10^3/μL. A manual differential showed a suppressed absolute neutrophil count (ANC) of 0.7 × 10^3/μL. A peripheral smear showed normocytic normochromic red blood cells, decreased white blood cells (WBCs), normal platelets, and occasional atypical lymphocytes but no malignant cells. Inflammatory markers were slightly elevated: erythrocyte sedimentation rate at 62 mm/h and C-reactive protein at 3.5 mg/dL. He also had elevated transaminases with aspartate aminotransferase at 131 U/L and alanine aminotransferase at 132 U/L. An extensive infectious workup, including blood cultures, urine cultures, sputum cultures, respiratory panel, acute hepatitis panel, HIV 1/2 antibody (Ab), HIV 1 RNA, HIV-p24 antigen (Ag), COVID-19 polymerase chain reaction, and Rapid Influenza A/B tests, were all unremarkable.

Due to his constellation of symptoms, he underwent a chest X-ray, as well as contrast-enhanced computed tomography scans of the chest, abdomen, and pelvis. All imaging studies were unremarkable for acute pathology. The echocardiogram revealed no abnormalities.

The patient received intravenous fluids and was started on empiric therapy with piperacillin-tazobactam. However, he continued to have fevers despite multiple days of empiric antibiotic therapy. On further investigation, the patient reported eating unpasteurized dairy products that were brought from the Dominican Republic. Brucellosis antibody screen was collected. His antibiotic regimen was changed to doxycycline. The following day, laboratory testing resulted positive IgG brucella antibodies. He was started on rifampicin 600 mg daily and doxycycline 100 mg twice daily for 8 weeks. Two days after targeted brucellosis therapy, the patient had an improved ANC of 1.1 × 10^3/μL and an improved WBC of 2.0 × 10^3/μL. He was discharged home with close follow-up. The patient had resolution of all symptoms, normalization of his WBC count, and resolution of transaminitis at his 8-week follow-up appointment.

Discussion

Brucellosis is a systemic zoonotic infection transmitted by contact with the fluids of infected animals or ingestion of their unpasteurized dairy products or undercooked meat[10]. The prevalence of brucellosis is estimated to be 15.53%[11]. The estimated annual incidence of brucellosis in the Americas is 3335. Central America has the highest risk of acquiring brucellosis, followed by South America (northern and southern parts of the continent), and finally North America[12]. Brucella melitensis is likely the most common cause of febrile neutropenia[13]. A study by Ozcay *et al* and Sari *et al* has reported four cases of febrile neutropenia, and brucella was the causative organism[14].

The diagnosis of brucellosis is challenging because clinical features resemble both infectious and non-infectious diseases[15]. It has a wide range of clinical presentations, from being asymptomatic to involving multiple organs[16]. The disease is classified based on the duration and severity of the symptoms into acute (less than 8 weeks), subacute (from 8 to 52 weeks), or chronic (more than 1 year). Localized disease is referred to when there is involvement of a single organ[17]. In a study conducted in Turkey involving 233 cases of brucellosis, findings indicated that 55% of patients experienced anemia, 21% had leukopenia, 26% showed thrombocytopenia, and 8% exhibited pancytopenia[18]. While the exact mechanisms are not fully understood, hypersplenism, hemophagocytosis, hemolysis, and granulomatous bone marrow lesions appear to be key factors contributing to these abnormalities in peripheral blood[19].

Systemic symptoms include insidious fever, sometimes with an irregular pattern (which is why this disease is also known as undulant fever), night sweats, myalgia, arthralgia, anorexia, depression, headaches, and lethargy[20]. The diagnosis of brucellosis requires the isolation of Brucella from blood or body tissues, or the combination of suggestive clinical presentation and positive serology. Tube and slide agglutination tests are used for diagnosis. Slide agglutination test is sensitive (>99%). However, the specificity of this test is low. It may be used as a screening test in the endemic regions[21]. Isolation of *Brucella* spp. from the clinical specimen is the gold standard because serological testing does not provide direct evidence for the presence of the pathogen[22,23].

The diagnosis is challenging due to the nature of bacteremia. During the treatment, two or three agents are combined. Due to the high recurrence rates, single-agent therapy that was previously employed is no longer used. Standard treatment entails administering 100 mg of doxycycline twice daily for 6 weeks and 1 g of streptomycin intramuscularly b.i.d. for 2 weeks. An alternate treatment plan can include 600–900 mg/day of rifampicin plus 100 mg of doxycycline twice a day. While the combination with rifampicin led to a higher recurrence rate, the combination with streptomycin has been demonstrated to be more successful[24]. However, the World Health Organization (WHO) recommends the use of doxycycline and rifampin likely due to the association with streptomycin, which is administered intramuscularly because of its poor oral absorption and associated risks[25]. Adding trimethoprim and sulfamethoxazole to current treatment plans improves success rates. Moreover, extending treatment to 6 weeks or more reduces recurrence risk compared to shorter regimens[26]. There are currently no universally accepted guidelines for treating immuno-compromised patients. Studies conducted in vitro have indicated a notable susceptibility to amikacin and third-generation cephalosporins[27,28].

In our literature review, we identified cases similar to ours, although they differed in presentations, immune status, other medical conditions, and initial treatments administered. Notably, only one case involved an immunocompetent individual. For instance, a case documented by Cuczzu *et al*[5] described a 2-year-old immunocompetent female with an ANC of less than 500 cells/mm^3. This highlights the rarity of febrile neutropenia in immunocompetent individuals compared to immunocompromised patients, who often present with common secondary diseases such as non-Hodgkin lymphoma, acute lymphoblastic leukemia, and acute myeloblastic leukemia, typically accompanied by significantly lower ANC values. This distinction underscores the importance of considering brucellosis in cases of febrile neutropenia, even among immunocompetent individuals, as demonstrated in the current case report (Table 1).

Our patient lived in a region where brucellosis was not endemic, but he was in close contact with the risk factors leading to infection. Increased awareness of brucellosis, specifically regarding its transmission sources and preventive measures, can help reduce its spread[29]. As there is currently no vaccine to protect humans against infection, brucellosis is a major health concern in underdeveloped nations. Developing an effective vaccination against Brucella is necessary due to the economic impact of infectious diseases on both humans and animals, as well as their clinical manifestations[30].

Table 1

Summary of literature review

Case report	Age (years)	Sex	Secondary medical condition	Immune status	Absolute neutrophil count (ANC) (cells/mm^3)	Empiric treatment	Definitive treatment
Arda *et al*[31]	56	Male	Non-Hodgkin lymphoma	Immuno-compromised	90/mm^3	Meropenem + Neutromycin + Teicoplanin + Amphotericin B	Doxycycline + Rifampin + Ciprofloxacin
	59	Male	Acute lymphocytic leukemia	Immuno-compromised	167/mm^3	Imipenem/Cilastatin + Teicoplanin	Not given
Cuczzu *et al*[5]	2	Female	No	Immuno-competent	<500/mm3	Cefuroxime and Meropenem + Clarithromycin	Trimethoprim-sulfamethoxazole (TMP-SMZ) + Rifampicin
Ozcay *et al*[14]	12	Female	Acute lymphoblastic leukemia	Immuno-compromised	Nil	Ceftazidime + Amikacin	Rifampin + Tetracycline
Ozbalci *et al*[20]	42	Female	Acute myeloblastic leukemia	Immuno-compromised	0/mm^3	Imipenem/Cilastatin + Ciprofloxacin + Teicoplanin	Doxycycline + Rifampicin
Metan *et al*[32]	17	Female	Acute lymphocytic leukemia	Immuno-compromised	300/mm^3	Cefepime + Amikacin and Piperacillin-Tazobactam	Doxycycline + Rifampin
Kasap *et al*[33]	8	Male	Acute lymphoblastic leukemia and Epididymoorchitis	Immuno-compromised	Nil	Meropenem + Vancomycin + Amikacin + Ornidazole + amphotericin-B	Doxycycline + Rifampicin +
Solmaz *et al*[34]	56	Male	Acute myeloblastic leukemia	Immuno-compromised	200/mm^3	Piperacillin/Tazobactam + vancomycin and Meropenem + Linezolid	Doxycycline + Rifampicin
Caglar Citak *et al*[13]	6	Male	Acute lymphoblastic leukemia	Immuno-compromised	100/mm^3	Meropenem + Amikacin + Teicoplanin + Amphotericin B and ciprofloxacin and linezolid	TMP-SMZ + Rifampicin
Sari R *et al*[8]	NA	NA	Malignancy	Immuno-compromised	NA	Cefepime + Amikacin	Streptomycin + doxycycline + TMP-SMZ

Empiric treatment: therapy when culture/serology results are pending; Definitive treatment: therapy when culture/serology results are definite; NA: not available.

Although systemic symptoms are a prevalent manifestation of brucellosis, febrile neutropenia is an uncommon manifestation. Brucellosis should be considered in the differential when determining the cause of febrile neutropenia. Early diagnosis of brucellosis and administration of the appropriate treatment typically result in a favorable outcome without complications.

Conclusion

A rare presentation of brucellosis is febrile neutropenia. It is critical to include zoonotic diseases in the differential of febrile neutropenia, even when initial cultures are unremarkable. A comprehensive patient history is instrumental in guiding appropriate laboratory testing, facilitating early diagnosis, and prompting the initiation of treatment. These findings emphasize the importance of maintaining a high index of suspicion for brucellosis and other zoonotic diseases in febrile neutropenic patients, leading to improved clinical outcomes and the prevention of potential complications.

Ethical approval

This case report, lefted on an individual patient, received approval from the Institutional Review Board.

Consent

We obtained written informed consent from the patient after explaining the study's purpose, potential risks and benefits, and the intended use of the data for publication. The patient was assured of privacy and willingly consented to the publication of this research.

Sources of funding

All the authors declare to have received no financial support or sponsorship for this study.

Author's contribution

F.M.K., conceptualization, methodology, project administration, and writing – original draft preparation; A.K., conceptualization, investigation, and writing – review and editing; S.R., A. R., methodology and writing – review and editing; A.Q., A.C., writing – original draft.

Conflicts of interest disclosure

All the authors declare to have no conflicts of interest relevant to this study.

Research registration unique identifying number (UIN)

Our case report is exempt from the registration requirements of the Declaration of Helsinki 2013, as it does not qualify as structured research involving human subjects. Case reports inherently left on individual patient experiences and do not necessitate a Unique Identifying Number (UIN) or registration in public databases. Nonetheless, our study adheres to ethical

standards and maintains transparency in line with relevant guidelines.

Guarantor

Fasih Mand Khan.

Data availability statement

The dataset supporting the conclusions of this article is included within the manuscript and is not publicly available due to privacy concerns; however, the corresponding author can be contacted for reasonable data access requests. We support ethical use and transparency in research.

Provenance and peer review

The paper was submitted unsolicited.

Acknowledgements

None.

References

[1] Pappas G, Akritidis N, Bosilkovski M, *et al*. N Engl J Med 2005;352. https://pubmed.ncbi.nlm.nih.gov/15930423/.
[2] Abd El-Wahab EW, Hegazy YM, El-Tras WF, *et al*. A multifaceted risk model of brucellosis at the human-animal interface in Egypt. Transbound Emerg Dis 2019;66:2383–401.
[3] Mantur B, Amarnath S, Shinde R. Review of clinical and laboratory features of human brucellosis. Indian J Med Microbiol 2007;25:188–202.
[4] Nejad RB, Krecek RC, Khalaf OH, *et al*. Brucellosis in the Middle East: current situation and a pathway forward. PLoS Negl Trop Dis 2020; 14:1–17.
[5] Cucuzza ME, Garozzo MT, Coco M, *et al*. Brucellosis: a rare cause of febrile neutropenia in a child. Pediatr Infect Dis J 2022;41:E430–3.
[6] Shemesh AA, Yagupsky P. Isolation rates of Brucella melitensis in an endemic area and implications for laboratory safety. Eur J Clin Microbiol Infect Dis 2012;31:441–43.
[7] Fruchtman Y, Segev RW, Golan AA, *et al*. Epidemiological, diagnostic, clinical, and therapeutic aspects of Brucella bacteremia in children in southern Israel: a 7-year retrospective study (2005-2011). Vector Borne Zoonotic Dis 2015;15:195–201.
[8] Sari R, Buyukberber N, Sevinc A, *et al*. Brucellosis in the etiology of febrile neutropenia: case report. J Chemother 2002;14:88–91.
[9] Sohrabi C, Mathew G, Maria N, *et al*. The SCARE 2023 guideline: updating consensus Surgical CAse REport (SCARE) guidelines. Int J Surg 2023;109:1136–40.
[10] Khan MZ, Zahoor M. An overview of brucellosis in cattle and humans, and its serological and molecular diagnosis in control strategies. Trop Med Infect Dis 2018;3:https://pubmed.ncbi.nlm.nih.gov/30274461/.
[11] Khoshnood S, Pakzad R, Koupaei M, *et al*. Prevalence, diagnosis, and manifestations of brucellosis: a systematic review and meta-analysis. Front Vet Sci 2022;9:976215.
[12] Laine CG, Johnson VE, Scott HM, *et al*. Global estimate of human brucellosis incidence. Emerg Infect Dis 2023;29:1789–97.
[13] Caglar Citak E, Arman D. Brucella melitensis: a rare cause of febrile neutropenia. Pediatr Hematol Oncol 2011;28:83–85.
[14] Özçay F, Derbent M, Ergin F, *et al*. Febrile neutropenia caused by Brucella melitensis in a child with hypoplastic acute lymphoblastic leukemia. Med Pediatr Oncol 2000;35:496-7.
[15] Araj GF. Human brucellosis: a classical infectious disease with persistent diagnostic challenges. Clin Lab Sci 1999;12:207-12.
[16] Colmenero JD, Reguera JM, Martos F, *et al*. Complications associated with *Brucella melitensis* infection: a study of 530 cases. Medicine (Baltimore) 1996;75:195–211.
[17] Doganay M, Aygen B. Human brucellosis: an overview. Int J Infect Dis 2003;7:173–82.
[18] Akdeniz H, Irmak H, Seçkinli T, *et al*. Hematological manifestations in brucellosis cases in Turkey. Acta Med Okayama. 1998;52:63–65.
[19] Al-Eissa YA, Assuhaimi SA, Al-Fawaz IM, *et al*. Pancytopenia in children with brucellosis: clinical manifestations and bone marrow findings. Acta Haematol 1993;89:132–36.
[20] Ozbalci D, Ergene U, Cetin CB. Brucellosis: a rare cause of febrile neutropenia in acute myeloblastic leukemia. Med Oncol 2011;28:255–57.
[21] Perry M, Bundle D Lipopolysaccharide antigens and carbohydrates of Brucella. 1990; https://www.cabidigitallibrary.org/doi/full/10.5555/19932283649
[22] Mangalgi S, Sajjan A. Comparison of three blood culture techniques in the diagnosis of human brucellosis. J Lab Physicians 2014;6:014–7.
[23] Akhvlediani T, Bautista CT, Garuchava N, *et al*. Epidemiological and clinical features of brucellosis in the Country of Georgia. PLoS One 2017;12:e0170376.
[24] Skalsky K, Yahav D, Bishara J, *et al*, Treatment of human brucellosis: systematic review and meta-analysis of randomised controlled trials. BMJ 2008;336:701-4.
[25] Al-Tawfiq JA. Therapeutic options for human brucellosis. Expert Rev Anti Infect Ther 2008;6:109–20.
[26] Al-Anazi KA, Al-Jasser AM. Brucella bacteremia in patients with acute leukemia: a case series. J Med Case Rep 2007;1:1–4.
[27] Bosch J, Linares J, De GMJL, *et al*. In-vitro activity of ciprofloxacin, ceftriaxone and five other antimicrobial agents against 95 strains of *Brucella melitensis*. J Antimicrob Chemother 1986;17:459–61.
[28] Samarina IV, Taran IF, Proskurina VA. Effekt vzaimodeĭstviia in vitro antibakterial'nykh preparatov v otnoshenii Brucella melitensis. Antibiotiki I Khimioterapiya. 1993;38:18–20.
[29] Abbasi-Ghahramanloo A, Ebrahimoghli R, Ebrahimnejad M, *et al*. Knowledge, attitudes, and practices regarding brucellosis in a rural population: a cross-sectional study. Heliyon 2024;10:https://pubmed.ncbi.nlm.nih.gov/38545216/.
[30] Karevan G, Ahmadi K, Taheri RA, *et al*. Immunogenicity of glycine nanoparticles containing a chimeric antigen as Brucella vaccine candidate. Clin Exp Vaccine Res 2021;10:35–43.
[31] Arda B, Tasbakan MI, Pullukcu H, *et al*. Brucella melitensis in the aetiology of febrile neutropenia: report of two cases brucellosis and febrile neutropenia. Int J Clin Pract 2007;61:1237–38.
[32] Metan G, Sardan YC, Hascelik G. Brucellosis in all patients with febrile neutropenia. Leuk Lymphoma 2006;47:954–56.
[33] Kasap T, Küpeli S. Brucella abortus causing febrile neutropenia together with epididymoorchitis. Indian J Pediatr 2016;83:1022–23.
[34] Solmaz S, Asma S, Özdocu H, *et al*. An unusual cause of febrile neutropenia: brucellosis. Mikrobiyol Bul 2014;48:669–73.