www.jmscr.igmpublication.org
Impact Factor (SJIF): 6.379
Index Copernicus Value: 79.54
ISSN (e)-2347-176x ISSN (p) 2455-0450
crossrefDOI: https://dx.doi.org/10.18535/jmscr/v6i8.162

IGM Publication
Journal Of Medical Science And Clinical Research
An Official Publication Of IGM Publication

Fever with pancytopenia: Ask and look to find the cause

Authors
H. Subramony M.D.[1], Mathi Manoj Kumar R[2]
Department of Internal Medicine, Apollo Hospitals, Chennai -6
Corresponding Author
Dr H Subramony
Consultant Physician, Apollo Hospitals, Greams Road, Chennai 600006, India
Email: *subbuaruna@rediffmail.com*, PH: 9841073910

Introduction

Brucellosis is the most common bacterial zoonotic disease encountered worldwide[1] and is endemic in the Mediterranean countries of Europe, north and east Africa, the Middle East, south and central Asia and Central and South America and yet it is often unrecognized and frequently goes unreported[2]. The infection is transmitted to humans by animals through direct contact with infected materials like afterbirth or indirectly by ingestion of animal products and by inhalation of airborne agents. Consumption of raw milk and cheese made from raw milk (fresh cheese) is the major source of infection in man. The bacterium survives for 6 weeks at 4° C in cream, 30 days in icecream, and 15 to 100 days in fresh cheese[3.4]. It is also an occupational disease for people who work in the livestock sector. It is also a Class B Bioterrorist agent[5] and is one of the highly neglected tropical diseases.

In India 80% of the population live in approximately 575,000 villages and thousands of small towns and have close contact with domestic animals[6]. Livestock plays an important role in the socio-economic life of India. The value output contribution from Indian Livestock sector to the GDP of the country was about 40.6% of total contribution from Agriculture and allied sector. As of 2000, the total value of output was estimated at about USD35 million[7]. With an estimated 86.8 million tons of annual milk production from animals managed by nearly 70 million farmers, India is the top-most milk producing country in the world[7]. But, the livestock industry practices in India are largely unregulated. Bovine brucellosis is common in India and has increased in recent times, perhaps due to increased trade and rapid movement of livestock[8].

The ability of brucellosis to mimic a myriad of infectious diseases and to involve any organ or system in the body had earned it a name "great imitator"[9]. Moreover, Brucellosis is under-diagnosed and underreported[10]. In addition to all that is said above, in a TB endemic country like India, an overlap in the clinical presentation has often led to wrong treatment.

The most important Brucella species in India are B. melitensis, and B. Abortus[6]. The clinical diversity of human Brucellosis ranges from asymptomatic disease to a fatal illness[11]. The

incubation period is 1-4 weeks, although it may extend beyond several months[12]. Infections with B. melitensis present more acutely than those with B.abortus[13]. The seroprevalence of human brucellosis varied widely from 0.8% to 26.6% in various studies[14-19].

Brucellosis has been one of the causes of PUO due to its nonspecific and myriad clinical presentations. Definite diagnosis of brucellosis requires the isolation of the organism from the blood, body fluids or tissues, but serological methods may be the only tests available in many settings[9,20]. Seropositivity for brucellosis was observed among 4.25%, 3.54%, 6.02% and 4.96% samples by RBPT, SAT, indirect ELISA and IgG ELISA, respectively in a study done in PUO cases by Pathak et al[21]. Positive blood culture yield ranges between 40% and 70%[22]. Culture proven Brucellosis was rarely reported in India with most earlier reports using serological studies to diagnose Brucellosis[23,24]. Hence, we report a culture proven case of human Brucellosis in a patient with a clinical presentation of PUO with pancytopenia.

Case Report

A 67 year old female from Melkolathur village, Thiruvannamalai, Tamil Nadu has come to our hospital with intermittent fever with chills, sweats, myalgias, and polyarthralgias of 3 weeks duration. The patient was evaluated elsewhere a week ago, where she reportedly had pancytopenia and was given empirical ceftriaxone, presuming the illness as enteric fever. Fever transiently subsided but returned within 4-5 days after which the patient was referred to our hospital.

Physical examination revealed pallor but was otherwise unremarkable. There were no signs of arthritis although the patient complained of polyarthralgias. Initial investigations revealed pancytopenia (Hb-10.9%, TLC-3400, Platelets-1 lakh). Liver function revealed mild transaminitis (ALT-47, AST-62), normal bilirubin, ALP and GGT levels. Blood smear for malarial parasite was negative. Leptospira and dengue serologies were negative. HIV ELISA was negative. Vitamin B12 was within normal limits. Ultrasonography of abdomen revealed moderate splenomegaly. CT scan of the abdomen revealed moderate splenomegaly with multiple focal hypo enhancing lesions. Bone marrow biopsy revealed normocellular marrow with microgranulomas.

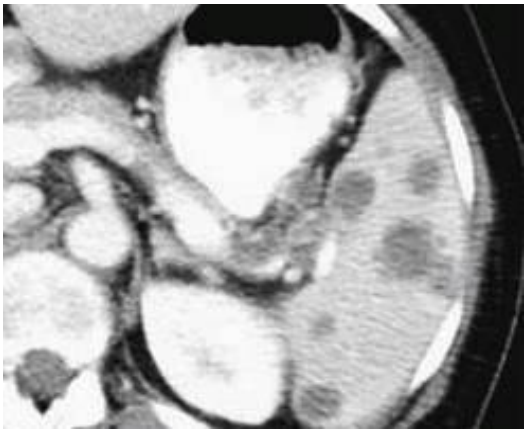

Fig 1: CT scan of abdomen showing hypodense lesions in Spleen

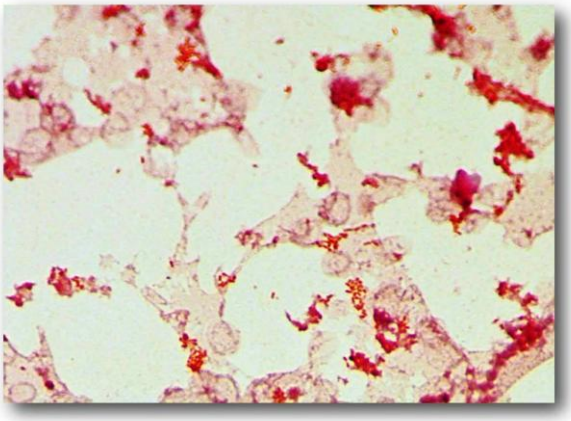

Fig 2: Blood smear gram stain showing gram negative coccobacilli

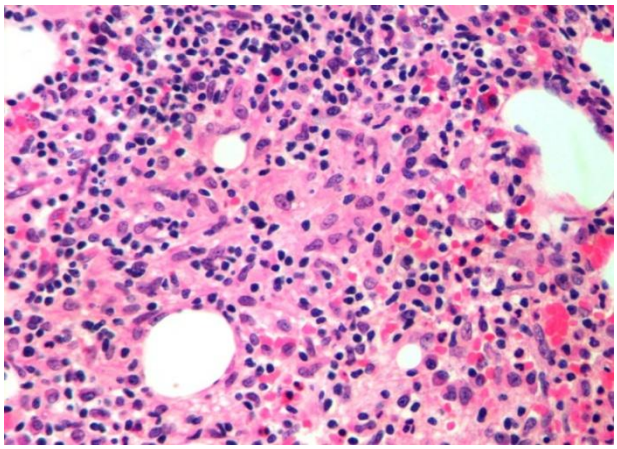

Fig 3: Ill formed microgranulomas

Blood culture grew Brucella melitensis. Patient was given Oral doxycycline and rifampicin for 6 weeks.

Discussion

Brucellosis is one of the earliest known diseases. Throughout history the disease has taken many different names, including Mediterranean Maltese, or Crimean fever and Bang's disease. It was named *undulant fever* after 1913 and then *brucellosis*, the name used today, from 1940 and onward[25-27].

Brucella species are small, non-encapsulated, non-motile, nonspore-forming, gram-negative, aerobic bacilli. Four species are pathogenic for humans: *Brucella abortus*, *B. melitensis* , *B. suis* , and *B. canis.* The most invasive and pathogenic type of human brucellosis is due *to B. melitensis followed by B. abortus and B. suis.* After entry to the human body and being taken by local tissue lymphocytes, *Brucellae* are later transferred through lymphatics to regional lymph nodes, then via the bloodstream to all organs of the body, particularly the reticuloendothelial system. The localization process of the organisms in body organs may be associated with inflammatory cellular infiltrates with or without granulomatous formation, caseation, necrosis or even abscess formation. Brucella is an intracellular microorganism that can survive inside the macrophages, where it has specific survival mechanisms. *Brucella* does not possess any defined endotoxin. The lipopolysaccharide layer on the cell wall shows endotoxic activity.

Brucellosis is a disease of protean manifestations that may simulate other febrile illnesses. Two features may provide a clue towards suspecting Brucellosis and probably differentiating it from other tropical illnesses such as typhoid and malaria are: firstly, left untreated the fever of brucellosis shows an undulating pattern that persists for weeks before the commencement of an afebrile period that may be followed by relapse and secondly, presence of musculoskeletal symptoms and signs. History of travel to endemic areas should be obtained, as well as the patient's occupational and recreational history. In a study done by Vishwanath Sathyanarayanan et al, patients mainly presented with fever (100%) while other symptoms reported were myalgia (31%), musculoskeletal symptoms (arthralgia, backache) (34%), headache (24%), gastrointestinal symptoms (nausea, vomiting, diarrhoea, constipation and pain abdomen (28%) and altered sensorium (4%)[28].

Diagnosis of brucellosis requires the assessment of medical history, clinical evaluation, and routine laboratory and radiologic tests combined with culture, serology, or polymerase chain reaction (PCR) assay. The routine laboratory tests like complete blood count, erythrocyte sedimentation rate, C-reactive protein, and liver function tests show wide patient variability and are not specific for the diagnosis[9]. Isolation of brucellae from blood, CSF, bone marrow, or joint fluid or from a tissue aspirate or biopsy sample is definitive, and attempts at isolation are successful in 50–70% of cases[29].

The haematological abnormalities of Brucellosis are nonspecific; leucopenia, leukocytosis, anemia, thrombocytopenia, thrombocytosis, and pancytopenia all had been reported[9,30,31,32]. In a study by Demir C et al, anemia, leukopenia, thrombocytopenia and pancytopenia were found in 81%, 58%, 46% and 21%, respectively[33]. In a study from a tertiary care hospital in South India by Vishwanath Sathyanarayanan et al, 57.3% patients had anemia, 14.7% had leucocytosis, while only 14.7% had leucopenia. Thrombocytopenia was observed in 33.8% patients while thrombocytosis in 2.94%[28].

Bone marrow cultures were found to be more sensitive in patients who received prior antibiotic therapy, which usually is the case and in chronic form of Brucellosis[34,35], although in our case we didn't feel the need to do bone marrow culture since blood cultures grew Brucella. In a study by Demir C et al, bone marrow examination revealed hypercellularity in majority (73%) of patients, while granulomas were observed in 25%[33].

Our case highlights the importance of a history of animal contact and having a high index of suspicion of Brucellosis in PUO cases presenting with pancytopenia and bone marrow granulomas.

Conclusions

PUO with pancytopenia in a Brucellosis endemic setting warrants high index of suspicion more so in presence of bone marrow granulomas. It is quite unusual to find negative bone marrow cultures in the face of positive blood cultures.

Most cases of brucellosis have been diagnosed based on serological studies and there are very few case reports of positive blood cultures. This case is unusual in that the bone marrow cultures were negative however, blood cutures were positive for Brucella melitensis.

References

1. Bosilkovski M, Dimzova M, Grozdanovski K. Natural history of brucellosis in an endemic region in different time periods. *Acta Clin Croat*. 2009;48:41-46.
2. http://www.who.int/csr/resources/publications/Brucellosis.pdf
3. Davies G, Casey A. The survival of *Brucella abortus* in milk and milk products. *Br Vet J*. 1973;129:345-353.
4. Nicoletti P. Relationship between animal and human disease. In: Young EJ, Corbel MJ, eds. *Brucellosis: Clinical and Laboratory Aspects*. Boca Raton, FL: CRC Press; 1989: 41-45.
5. Greenfi eld RA, Drevets DA, Machado LJ. Bacterial pathogens as biological weapons and agents of bioterrorism. Am J Med Sci 2002; 323: 299-315.
6. J. Biosci. 33(4), November 2008, 539–547, © Indian Academy of Sciences
7. http://www.fao.org/docrep/article/agrippa/657_en.htm
8. Renukaradhya, G., Isloor, S. and Rajasekhar, M. (2002). Epidemiology, zoonotic aspects, vaccination and control/eradication of brucellosis in India. Veterinary Microbiology, 90(1-4), pp.183-195.).
9. Franco MP, Mulder M, Gilman RH, et al. Human brucellosis. *Lancet Infect Dis*. 2007;7:775-786.
10. Franco MP, Mulder M, Gilman RH, Smits HL. Human brucellosis. Lancet Infect Dis 2007; 7(12):775-786.
11. 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.
12. Mandell, G. and Douglas, R. (2015). *Mandell, Douglas, and Bennett's principles and practice of infectious diseases*. 8th ed. Philadelphia, Pa: Elsevier, Saunders, p.2585.
13. Troy SB, Rickman LS, Davis CE. Brucellosis in San Diego: epidemiology and species-related differences in acute clinical presentations. *Medicine (Baltimore)*. 2005;84: 174-187.
14. Kadri SM, Ruksana A, Laharwal MA, Tanvir M. Seroprevalence of brucellosis in Kashmir [India] among patients with pyrexia of unknown origin. J Indian Med Assoc 2000;98:170-1.
15. Sharma VD, Sethi MS, Yadav MP, Dube DC. Sero-epidemiologic investigations on brucellosis in the states of Uttar Pradesh [U.P.] and Delhi [India]. Int J Zoonoses 1979;6:75-81.
16. Appannanavar SB, Sharma K, Verma S, Sharma M. Seroprevalence of Brucellosis: A 10-year experience at a tertiary care center in north India. Indian J Pathol Microbiol 2012;55:271-2.
17. Priyadarshini A, Sarangi LN, Palai TK, Panda HK, Mishra R, Behera PC. Brucellosis in cattle and occupationally exposed human beings: A Serosurvey in Odisha, India. J Pure Appl Microbiol 2013;7:3255-60.

18. Agasthya AS, Isloor S, Prabhudas K. Brucellosis in high risk group individuals. Indian J Med Microbiol 2007;25:28-31.
19. Yohannes M, Gill JP. Seroepidemiological survey of human brucellosis in and around Ludhiana, India. Emerg Health Threats J 2011;4:7361.
20. Al Dahouk S, Nöckler K. Implications of laboratory diagnosis on brucellosis therapy. Expert Rev Anti Infect Ther 2011;9:833–45.
21. Pathak AD, Dubal ZB, Doijad S, et al. Human brucellosis among pyrexia of unknown origin cases and occupationally exposed individuals in Goa Region, India. *Emerging Health Threats Journal*. 2014;7:10.3402/ehtj.v7.23846. doi:10.3402/ehtj.v7.23846.
22. Farrar, J. and Manson, P. (2014). *Manson's Tropical diseases*. 23rd ed. elsevier, p.376.
23. J Assoc Physicians India. 2007 Apr; 55:271-5. Hospital-based case series of 175 cases of serologically confirmed brucellosis in Bikaner. Kochar DK, Gupta BK
24. Prasad, S. and Tanveer, K. (2013). Brucella infections in high-risk population and in patients hospitalized for fever: A serological study at Kolar, Karnataka. *Annals of Tropical Medicine and Public Health*, 6(5), p.549.
25. Vassallo DJ. The corps disease: brucellosis and its historical association with the Royal Army Medical Corps. *J R Army Med Corps*. 1992;138:140-150.
26. Piqueras M. Microbiology: a dangerous profession? *Int Microbiol*. 2007;10:217-226.
27. Hall WH. Brucellosis. In: Evans AS, Brachman PS, eds. *Bacterial Infections of Humans, Epidemiology and Control*. 2nd ed. New York: Plenum; 1991:133-149.
28. Sathyanarayanan, V. and Razak, A. (2011). Clinical profile of brucellosis from a tertiary care center in southern India. *Asian Pacific Journal of Tropical Medicine*, 4(5), pp.397-400.
29. Hauser, S., Longo, D., Loscalzo, J. and Harrison, T. (2015). *Harrison's principles of internal medicine*. 19th ed. McGraw-Hill, pp.194e-2.
30. Pappas G, Akritidis N, Bosilkovski M, et al. Brucellosis. *N Engl J Med*. 2005;352:2325-2336.
31. Buzgan T, Karahocagil MK, Irmak H, et al. Clinical manifestations and complications in 1028 cases of brucellosis: a retrospective evaluation and review of the literature. *Int J Infect Dis*. 2010;14:e 469-e478.
32. Calik S, Gokengin D. Human brucellosis in Turkey: a review of the literature between 1990 and 2009. *Turk J Med Sci*. 2011;41:549-555.
33. Chin Med J (Engl). 2012 Jun;125 (11): 1871-6. Bone marrow biopsy findings in brucellosis patients with hematologic abnormalities. Demir C , Karahocagil MK
34. Christopher S, Umapathy BL, Ravikumar KL. Brucellosis: review on the recent trends in pathogenicity and laboratory diagnosis. *J Lab Physicians*. 2010;2:55-60.
35. Gotuzzo E, Carrillo C, Guerra J, et al. An evaluation of diagnostic methods for brucellosis—the value of bone marrow culture. *J Infect Dis*. 1986;153:122-125.