Fever with pancytopenia: Ask and look to find the cause

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Introduction
Brucellosis is the most common bacterial zoonotic disease encountered worldwide¹ 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 unreported². 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 cheese³⁴. It is also an occupational disease for people who work in the livestock sector. It is also a Class B Bioterrorist agent⁵ 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 animals⁶. 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 million⁷. 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 world⁷. 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 livestock⁸. 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 underreported¹⁰. 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. Abortus⁶. The clinical diversity of human Brucellosis ranges from asymptomatic disease to a fatal illness¹¹.
incubation period is 1-4 weeks, although it may extend beyond several months. Infections with B. melitensis present more acutely than those with B.abortus. The seroprevalence of human brucellosis varied widely from 0.8% to 26.6% in various studies.

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. 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. Positive blood culture yield ranges between 40% and 70%. Culture proven Brucellosis was rarely reported in India with most earlier reports using serological studies to diagnose Brucellosis. 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. 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 onward25-27.

*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%).

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 diagnosis9. 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 cases28. The haematological abnormalities of Brucellosis are nonspecific; leucopenia, leukocytosis, anemia, thrombocytopenia, thrombocytosis, and pancytopenia all had been reported9,30,31,32. In a study by Demir C et al, anemia, leukopenia, thrombocytopenia and pancytopenia were found in 81%, 58%, 46% and 21%, respectively33. 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 Brucellosis34,35, 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 cultures were positive for Brucella melitensis.

References