Recurrent Pyrexia, Brucellosis, Underdiagnosis: The Puzzle Triad Untangled By Blood Cultures – The Benchmark Tool Coming To Aid

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Abstract :

Introduction: Human brucellosis, a zoonotic disease is common in India. In spite of high prevalence, the disease usually remains under diagnosed or misdiagnosed. **Aim:** To evaluate & establish the significance of blood culture for diagnosis of brucellosis. **Materials & Method:** A study of 10 patients of brucellosis diagnosed by blood culture were evaluated retrospectively, for the various clinical & laboratory profiles, during the period of 2014-17. **Results:** All the ten patients, positive for brucellosis by blood culture were having history of fever. Other clinical presentations were - abdominal pain (n=6,60%), vomiting (n=5,50%), headache (n=1,10 %), generalized body ache (n=1,10%), anorexia (n=1,10%), joint pain (n=1,10%), cough (n= 1,10%), mild splenomegaly (n=2,20%), mild hepatomegaly (n=1,10%), mild to gross hepatosplenomegaly (n=3,30%). In all the cases, Brucella spp. were recovered from patient's blood culture & identified within 7 days of sample collection. The time-to- detection of BACTEC blood culture system (positive indication) was 3-5 days. **Conclusion:** A high level of clinical suspicion & proper blood culture remains the gold standard for early diagnosis of brucellosis.

Key words : Blood culture, Brucella, Human Brucellosis.

Introduction :

Human Brucellosis, a zoonosis, has been reported from many states of India such as Karnataka, Rajasthan, J & K, Andhra Pradesh, Punjab, Maharashtra, Gujarat etc.[1-7] Brucellosis is mainly a disease of animals including cattle, goats, sheep, camels, dogs & pigs.[8]

Human brucellosis is transmitted through ingestion of unpasteurized milk & dairy products, ingestion of raw meat, direct contact with infected animals or inhalation of infectious airborne animal manure. Occupational exposure of veterinarians and laboratory personnel can result in transmission of the disease through contaminated aerosols. Other rare possible modes of transmission are blood transfusion, tissue transplantation and sexual.[1,8] The clinical presentation of brucellosis is vague & often non-specific. Common symptoms are fever, night sweats, chills, malaise; often accompanied by headache, myalgia & arthralgia.[9] In the laboratory, diagnosis of brucellosis is possible by culture examination & serological test. But isolation of bacteria from blood culture or body fluids provides the definitive proof of brucellosis.[8]

In spite of the high prevalence of brucellosis in animals and presence of favorable factors for transmission to human beings, the exact burden of the disease is not known in Gujarat.[7,10-12] Here, we present 10 cases of brucellosis, focusing on clinical findings, exposure history, laboratory parameters, and treatment.

Methods:

During the period of three years (2014-17), total 6866 blood culture samples, from different clinical departments, were received at microbiology laboratory for evaluation of infectious conditions. Out of these, a total of 10 samples turned out to be positive for brucellosis. As all patients presented with fever, blood cultures were obtained from all in BACTEC blood culture vials, prior to antibiotic administration. All the blood culture vials were incubated in BACTEC blood culture 9050 machine.

The positive blood culture vials were subcultured onto blood agar, chocolate agar & MacConkey agar plates. Colonies of Brucella on blood agar & chocolate agar were observed after 36-48 hours of incubation in the candle jar. All the isolates were confirmed as Brucella spp. by biochemical reactions i.e. catalase test positive, oxidase test positive & a positive urease test in less than 2 hours. [9]

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Apart from blood culture, all the patients were also investigated for enteric fever by widal test, malaria, dengue fever, rheumatoid arthritis, tuberculosis & urinary tract infections (UTIs), but all the tests were negative.

All the 10 positive cases of brucellosis were analyzed for following variables: age, gender, history of exposure to the source of infection, clinical features, previous admissions, imaging techniques, microbiological & other laboratory parameters.

Results:

Out of the total 10 blood culture positive cases of brucellosis, 9 (90%) were of pediatric age group (3-14 years) & 1 (10%) was an adult patient (50 years). There were 5 females & 5 males. All the patients were from rural area.

The most predominant clinical manifestation was fever (n=10,100%). Other clinical manifestations were abdominal pain (n=6,60%) & vomiting (n=5,50%), headache (n=1,10%), generalized bodyache (n=1,10%), anorexia (n=1,10%), cough (n=1,10%). On ultrasound examination, two (20%) patients had mild splenomegaly, one (10%) had mild hepatomegaly, three (30%) had mild to gross hepatosplenomegaly, and one (10%) had mild ascites.

Majority of the patients had mild anemia (n=8,80%), decreased white blood cell count (n= 5,50%). Only one (10%) patient showed neutrophilic leukocytosis. Low platelet count less than 1, 50,000/cmm was seen in four (40%) patients. Erythrocyte sedimentation rate was mildly elevated in four (40%) patients. Liver function was altered in the form of raised SGPT, SGOT or alkaline phosphatase in five (50%) cases.

The only evidence of brucellosis in these patients was blood culture positive with supportive demographic & clinical parameters.

Discussion:

The true incidence of human brucellosis is unknown for most countries including India because of misdiagnosis & under-reporting. Alertness of clinicians and close collaboration with the microbiologists are essential even in endemic areas to correctly diagnose and treat protean human brucellosis. [13]

Acute brucellosis resembles a viral illness with fever, anorexia, myalgia, arthralgia, night sweats and may be complicated by orchitis, meningo-encephalitis or infective endocarditis. Chronic brucellosis is primarily a disease of joints with spondylitis, sacroiliitis and peripheral arthritis. Sequel of disease may be orchitis, uveitis, meningitis and granulomatous hepatitis. [6]

Recurrent fever is the most common clinical manifestation of brucellosis & it occurs due to periodic release of bacteria from reticulo-endothelial (RE) system.[9] In present study also, recurrent fever was observed as one of the commonest presentation – three (30%) cases presented with a fever of less than 7 days duration, six (60%) with fever of 7-30 days & one (10%) with fever of more than 30 days. The fever was associated with chills & rigors in four (40%) patients. Four (40%) patients were hospitalized earlier also on two occasions, with a similar febrile illness but they did not respond to the treatment.

Two patients in our study, presented with unusual manifestations.

1. One presented with fever, joint pain & difficulty in walking; he was registered & visited orthopedic OPD for the same. USG of the knee joint showed synovial effusion & X-ray showed growth arrest line in the lower end of femur. This may be a case of chronic brucellosis.
2. A 50 year old lady presented with fever, anaemia & thrombocytopenia mimicking dengue fever.

Because of varied & unusual manifestations & with lack of clinical suspicion, brucellosis is often misdiagnosed. In present study, 9 out of 10 cases were initially diagnosed either as enteric fever, acute viral hepatitis, iron deficiency anemia, synovitis, dengue fever or fever of unknown origin. Brucellosis was suspected in only one patient at his first visit. Similarly, in many other studies in India & worldwide, misdiagnosis of brucellosis was quite common.[2,14,15]

Brucella primarily infects organs of the RE system, such as lymph nodes, spleen, liver & bone marrow which leads to various types of hematological abnormalities, lymphadenopathy, splenomegaly, & hepatomegaly. The liver is commonly involved in brucellosis, although liver function tests can be normal or only mildly elevated.[8, 9, 16] Hematological abnormalities like mild anemia, mild leucopenia or normal white blood cell count; slightly raised liver enzymes & findings of hepato-splenomegaly were observed in our study & previous

studies too.[1,5,15] These findings gave an important clue for the diagnosis of brucellosis. History of exposure to the source of infection is important as it can alert clinicians to the possibility of brucellosis.[15] In present study, three cases showed history of ingestion of unpasteurized sheep/ goat milk & one showed history of close contact with dog. We were unable to trace history of exposure in six cases because brucellosis was not suspected at the time of admission & they had been discharged before the blood culture vial became positive for growth.

In the past, isolation of Brucella was hindered by the slow growth of the organism and the lack of a suitable commercial blood culture system. The modern automated continuous-monitoring blood culture systems (BACTEC / BacT Alert) have improved the speed of detection (3-5 days); as compared to the old conventional methods (1-2 weeks). In present study, all the Brucella isolates were recovered from blood culture within 7 days. Time-to-detection of BACTEC blood culture was 3 days in one case, 4 days in six cases & 5 days in three cases (mean time 4.2 days). The time-to-detection was $\leqslant$ 5days & $\leqslant$ 7days by BACTEC method in many previous studies. [17,18,19] Two cases were treated with a combination of cotrimoxazole & rifampicin, one was treated with a combination of ciprofloxacin & rifampicin and one was treated with a combination of amikacin & doxycycline according to the WHO guidelines.[8] They all responded well with the medical treatment only. However, unfortunately we lost six cases as they did not come for follow up.

Conclusion:

The commonest diseases are generally the first ones provisionally diagnosed, in the patients with prolonged pyrexia & nonspecific symptoms. But if the patients are not responding to the treatment, it is recommended that a new spectrum of diseases must be included in the list of differential diagnosis. Considering brucellosis as the flag-bearer in this group won't be an exaggeration.

A rural background and a constant and close contact with the livestock is a very essential history to be elicited to suspect any zoonoses, more so in cases of brucellosis. Also, recurrent febrile illnesses poorly responding to antibiotics should ring a bell of suspicion. Other findings like complete blood count, liver function tests, ultrasound examination can help to support the diagnosis.

Correct diagnosis of brucellosis is not possible without Microbiological investigations. The importance of taking samples for blood culture before the initiation of antibiotic therapy can't be overemphasized in all the ten cases, especially in the atypical ones. Hence, blood culture is used as the first diagnostic tool in cases of prolonged pyrexia in our hospital. Despite many drawbacks of serological tests, they can be used for presumptive diagnosis; however, as the present study indicates, blood culture should remain gold standard for diagnosis of brucellosis. High level of clinical suspicion, proper blood culture techniques especially by automated blood culture system & good laboratory practice would help for the early diagnosis & proper management of brucellosis.

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