

Case Report

A case of PUO-Human Brucellosis

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Abstract

Brucellosis is a zoonosis and the infection is almost invariably transmitted by direct or indirect contact with infected animals or their products. It is essentially a disease of animals, especially domesticated livestock, caused by bacteria of the *Brucella* group with humans as an accidental host. The human disease usually manifests itself as an acute febrile illness which may persist and progress to a chronically incapacitating disease with severe complications. The clinical picture is not specific and requires support with the laboratory tests. In absence of specific treatment, the disease may persist for weeks or months leading to cardiovascular and neurological complications. The duration of the human illness and its long convalescence means that brucellosis is an important economic as well as a medical problem for the patient because of time lost from normal activities. Our case is a 35 year old male farmer presenting with fever and behavioural disturbances, an atypical presentation, which would have been misdiagnosed without high index of suspicion. Thus it emphasizes that physicians should consider the diagnosis of Brucellosis in certain groups like farmers, farm workers, shepherds, veterans, laboratory workers, etc.

Keywords: Brucellosis, zoonosis, farmers, laboratory workers

1. Introduction

Brucellosis is a zoonotic infection caused by the bacterial genus *Brucella*. The bacteria are transmitted from animals to humans by ingestion through infected milk and milk products, direct contact with an infected animal, or inhalation of aerosols¹. Humans are accidental hosts, but brucellosis continues to be a major public health concern worldwide and is the most common zoonotic infection¹. *Brucella* is disseminated via hematogenous route with a focal localization in various organ systems. With a wide spectrum of clinical manifestations, it can affect any organ or tissue in the human body. The most commonly affected systems are the musculoskeletal, gastrointestinal, genitourinary, hematological, respiratory and cardiovascular systems². Neuropsychiatric symptoms like headache, depression, altered behaviour and fatigue are not uncommon despite the rare involvement of the nervous system³.

In spite of its worldwide distribution, the fact of being considered endemic in some locations, and because of its broad spectrum of clinical manifestations—therefore having many differential diagnoses, both infectious and non-infectious⁴, brucellosis remains under diagnosed and underreported⁵.

The purpose of this paper is to report such a case of brucellosis that presented with neuropsychiatric symptoms during its course but not associated with neurological involvement.

2. Case Report

A 35 year male, with an occupation of farming and cattle rearing practices presented with fever and altered behaviour. Fever was typically intermittent, high grade and associated with chills for last one month. He had history of psychotic behaviour of sudden onset for 2 days and hence was referred to our centre. He also had history of backache and headache for last 1 month.

No history of evening rise of temperature, night sweats, significant weight loss.

No history of convulsions, vomiting, pain in abdomen, burning micturition, cough, breathlessness, chest pain or palpitation.

No history of past medical and psychiatric illness.

Chronic alcoholic since 10 years, abstinence since 1 month. History of regular consumption of raw and unpasteurized milk and milk products.

Appetite is decreased. Bowel/Bladder-normal and sleep-normal.

2.1 On Examination

He is conscious, aggressive.

Febrile-101F; Pulse is 100/min regular; Blood pressure is 110/70mmHg.

Pallor present but no icterus, lymphadenopathy, clubbing, cyanosis or edema.

Dehydration +++

No petechiae/purpura.

2.2 Systemic Examination

CNS-Terminal neck stiffness present, DTR-present, Power-V/V in all limbs,

Plantar response-Flexor, Pupils-Both normal in size reacting to light.

Other systems were within normal limit. A psychiatric opinion was sought. An organic cause for acute psychosis was most likely.

Based on the presentation, the following D/D were considered,

1. Enteric fever,
2. Cerebral malaria,
3. CNS Tuberculosis,
4. Brucellosis,
5. Connective tissue disorder.

He was thoroughly investigated-

Table No.1: Investigation report

Investigation	Lab Value	Reference Range
Hemoglobin	8.9gm/dl	13.8-17.2gm/dl
Total White Count	4200cells/mm ³	3500-10500/mm ³
Platelet count	3,00,000cells/mm ³	1.5-4.5lakh/mm ³
Liver Function Test	Normal	--
Renal Function Test	B.urea-25mg/dl Sr Creatinine-1.1 mg/dl	10-45mg/dl 0.6-1.5mg/dl
Serum Electrolytes	Na- 145mEq/L K- 4.4mEq/L	135-145mEq/L 3.5-4.5mEq/L
ESR	20mm/hr	<15mm/hr
HIV	Negative	-
HBsAg	Negative	-
VDRL	Negative	-
CSF	Protein-0.2mg/dl Sugar-70mg/dl Cells:RBCs-3;WBCs-10 CSF-ADA-negative	0.18-0.45mg/dl 40-80mg/dl WBCs<3 -
PS for Malarial Parasite	Absent	-
Rapid Malarial Test	Negative	-
Widal Test	Negative	-
CXR	No abnormality	-
USG(Abdomen/Pelvis)	Mild hepatosplenomegaly	-
CT Scan(Plain/Contrast)	Normal	-
ECG	Normal	-

Patient was started on IV Broad-spectrum antibiotics, anti-pyretics and analgesics for backache. He was given mild sedation and was restrained physically for aggressive behaviour. Despite of the treatment, fever recurred daily and disorientation increased. His *B. Melitensis* Slide agglutination test came to be positive with the high titre of 1:320.

Empirical antimicrobial therapy was initiated for brucellosis with Cap. Doxycycline (200mg/day). Awaited Blood culture also came to be positive for *B. Melitensis* thus confirming the diagnosis. Inj.Streptomycin (750mg)IM was hence added to the above regimen. He responded well to treatment and thus further investigations like ANA, DsDNA were not carried out.

An X-ray Thoraco-Lumbar spine was done to rule out any vertebral involvement, but was normal.

Thus based on – 1) H/O Relapsing fever;

- 2) Occupational history with exposure to domesticated livestock and consumption of raw, unpasteurised milk;
- 3) Musculoskeletal symptoms like backache;
- 4) Laboratory evidence of High Brucella titre and Positive blood culture.

a diagnosis of **Human Brucellosis** was confirmed.

He was discharged and maintained at the following regimen-

1. Inj. Streptomycin 0.75gm IM for 21 days
2. Cap. Doxycycline 100mg p.o Bd for 6 weeks.

On follow-up, the patient was asymptomatic, afebrile and had resumed his routine activities.

Our patient had presented with Fever with Acute psychosis which is an unusual presentation of Brucellosis and hence would have been misdiagnosed. These unusual features of brucellosis may be underestimated components of the disease.

3. Discussion

3.1 Human Brucellosis

Brucellosis is a bacterial zoonosis transmitted directly or indirectly to humans from infected animals, predominantly domesticated ruminants and swine⁶. The disease has various names including Mediterranean fever, Malta fever and gastric remittent fever. It is also called as *undulant fever* because of its remittent character⁶. *Brucella* organisms, which are small aerobic intracellular *coccobacilli*, localize in the reproductive organs of host animals, causing abortions and sterility. They are shed in large numbers in the animal's urine, milk, placental fluid, and other fluids. To date, 8 species have been identified, named primarily for the source animal or features of infection. Of these, the following 4 have moderate-to-significant human pathogenicity⁶:

1. *Brucella melitensis* (from sheep; highest pathogenicity)
2. *Brucella suis* (from pigs; high pathogenicity)
3. *Brucella abortus* (from cattle; moderate pathogenicity)
4. *Brucella canis* (from dogs; moderate pathogenicity)

3.1.1 Epidemiology

Brucellosis causes more than 500,000 infections per year worldwide. Its geographic distribution is limited by effective public and animal health programs, and the prevalence of the disease varies widely from country to country¹.

3.1.2 Modes of Transmission

1) Ingestion; 2) Inhalation; 3) Mucosal or percutaneous exposure; 4) Person-to-person (rare)⁶

Human Brucellosis is usually associated with accidental occupational or domestic exposure to infected animals or their products⁶.

3.1.3 High-risk groups- Farmers, shepherds, goatherds, veterinarians, laboratory workers and employees in slaughter houses and meat-processing plants⁶.

3.2 Pathogenesis

- i. *Brucella* can gain entry into the human body through breaks in the skin, mucous membranes, conjunctivae, and respiratory and gastrointestinal (GI) tracts.
- ii. Once within the bloodstream, the organisms quickly become intracellular pathogens contained within circulating polymorphonuclear cells (PMNs) and macrophages, making use of numerous mechanisms to avoid or suppress bactericidal responses.
- iii. The organism is a "stealth" pathogen whose survival strategy is centered on processes that avoid triggering innate immune responses and permit survival within the monocytes⁶. The smooth *Brucella* LPS, plays a key role in pyrogenicity and in resistance to phagocytosis⁶.
- iv. Brucellae that survive are transported into the lymphatic system and may replicate there locally; they also may replicate in the kidney, liver, spleen, breast tissue, or joints, causing both localized and systemic infection.

3.3 Clinical Features

3.3.1 Incubation period- 1 week to several months⁶.

The fever of brucellosis shows an undulating pattern that persists for weeks before commencement of an afebrile period that may be followed by relapse. It is usually associated with profuse sweats, especially at nights⁶.

Fever of unknown origin (FUO) is a common initial diagnosis in patients in areas of low endemicity⁷.

Constitutional symptoms of brucellosis include anorexia, asthenia, fatigue, weakness, and malaise, and weight loss and are very common (> 90% of cases).

3.3.2 Musculoskeletal involvement

The most common are musculoskeletal pain and physical findings in the peripheral and axial skeleton (40% of cases). Osteomyelitis more commonly involves the lumbar and low thoracic vertebrae than the cervical and high thoracic spine. Individual joints that are most commonly affected by septic arthritis are the knee, hip, sacroiliac, shoulder, and sternoclavicular joints; the pattern may be one of monoarthritis or polyarthritis. Osteomyelitis may also accompany septic arthritis. Hence, Tuberculosis of spine should be always ruled out.

3.3.3 Gastro-intestinal involvement

A significant percentage (approximately 50%) of patients has gastrointestinal (GI) complaints, primarily dyspepsia, abdominal pain (less common), hepatosplenomegaly (one-quarter patients) and lymphadenopathy (10-20%). Hepatic abscesses and Spontaneous bacterial peritonitis secondary to brucellosis infection has been reported. Constipation, diarrhea, and vomiting may occur.

3.3.4 Cardiovascular involvement

Endocarditis from brucellae (~1%) affecting aortic valve commonly (native and prosthetic) is reported, with septic embolization a common complication of this form of brucellosis. Other cardiac complications, such as pulmonary edema or dysrhythmias, are rare. *Brucella* endocarditis is the form most commonly associated with fatalities.

3.3.5 Neurobrucellosis

It refers to a variety of neurological complications associated with brucellosis. Direct invasion of the central nervous system occurs in about 5% of cases of *B. melitensis* infection, and meningitis or meningo-encephalitis are the most common manifestations. *Brucella* meningitis can be acute or chronic. Analysis of cerebrospinal fluid (CSF) usually reveals elevated protein content, normal or low glucose concentration, and a lymphocytic pleocytosis.

Other CNS manifestations of brucellosis include cerebral vasculitis, mycotic aneurysms, brain and epidural abscesses, infarcts, haemorrhage, and cerebellar ataxia. Peripheral nerve complications include neuropathy/radiculopathy, Guillain-Barré syndrome, and a poliomyelitis-like syndrome.

Our patient had presented with acute psychosis, but his CSF picture was non-conclusive. This suggests that though rarely but brucellosis can present with neuropsychiatric symptoms without even actual involvement of CNS. Similarly it can spread throughout the body to infect almost every organ including respiratory, genito-urinary, skin and eye⁸.

3.4 Diagnostic Work-up

1) All routine investigations like hemogram, LFT, RFT, etc

2) **Culture-** Diagnosis of brucellosis is definitive when *Brucella* organisms are recovered from blood, bone marrow, or other tissue. Because the reticuloendothelial system holds a high concentration of brucellae, bone marrow culture is thought to be the criterion standard. Sensitivity is usually 80-90%⁹.

3) **Serology-** Serologic testing is the most commonly used method of diagnosing brucellosis. Repeated serologic testing is recommended if the initial titer is low.

The tube agglutination test is the most popular test tool for the diagnosis of brucellosis. Titers higher than 1:160 in conjunction with a compatible clinical presentation are considered highly suggestive of infection.

Enzyme-linked immunosorbent assay (ELISA) typically uses the cytoplasmic proteins as antigens and measures IgM, IgG, and IgA is also used¹⁰.

4) **Polymerase chain reactions** also used.

5) CSF-analysis, Neuro-imaging and spinal X-ray are done to rule out Neurobrucellosis.

3.5 Treatment⁶

A. Gold Standard (uncomplicated) regimen – Inj. Streptomycin 0.75-1 gm IM for 14-21 days PLUS Cap. Doxycycline 100mg p.o BD for 6 weeks

Alternative (WHO-recommendation) regimen – Cap. Doxycycline 100mg p.o BD PLUS Cap. Rifampin 450mg p.o BD for 6 weeks

B. Complicated (Endocarditis, Neurobrucellosis)

Triple drug regimen including an initial course of an aminoglycoside (streptomycin) combined with rifampin and doxycycline for 6 months. Inj. Ceftriaxone 1-2 gm IV 12 hourly can be added effectively as a supplementation to the above standard regimen.

3.6 Prognosis

Relapse occurs in up to 30% of poorly compliant patients. Mortality is less than 1%. Death is usually a consequence of cardiac involvement.

3.7 Prevention and patient education⁶

Vaccine based on live attenuated *Brucella* strains, such as *B. abortus* 19BA or 104M and *B. Melitensis* strain 16M have been tried but use is limited due to short-term efficacy and high reactivity.

Promoting animal vaccination, control of animal movement, protective devices for the lab workers, general awareness, hygienic farming and rearing practices and pasteurization of all milk products can help in preventing animal-to-human transmission.

4. Conclusion

Our case is unique and interesting due to unusual presentation of Brucellosis as fever with acute psychosis, which without high index of suspicion would have led to erroneous diagnosis. Our report emphasizes the need to remind clinicians to consider brucellosis in the differential diagnosis of unexplained febrile illness. We also hope to inspire clinicians to obtain information about patient activities including travel, food-consumption, occupation and outdoor recreation such as wild-swine hunting. Early identification and diagnosis of Brucellosis can help to prevent significant mortality and morbidity.

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