An Unusual Etiology of PUO

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Abstract
Infection with Brucella spp. continues to pose a human health risk globally despite strides in eradicating the disease from domestic animals. Brucellosis has been an emerging disease since the discovery of Brucella melitensis by Sir David Bruce in 1887. Although many countries have eradicated B. abortus from cattle, in some areas B. melitensis and B. suis have emerged as causes of this infection in cattle, leading to human infections. Currently B. melitensis remains the principal cause of human brucellosis worldwide including India.

Introduction
Brucellosis in endemic and non-endemic regions remains a diagnostic puzzle due to misleading non-specific manifestations and increasing unusual presentations. Fewer than 10% of human cases of brucellosis may be clinically recognized and treated or reported.

Brucellosis is a zoonosis transmitted to humans from infected animals. A type of fever characterized by fairly regular remissions or intermissions has been recognized along the Mediterranean littoral since the time of Hippocrates in 450 B.C. Much later in the 19th century, the disease was found to affect British armed forces and the local population of Malta. J. A. Marston, an assistant surgeon of the British Medical Department working in the Mediterranean in 1861, first described the symptoms of brucellosis in himself as “gastric remittent fever.” The cause of this disease was obscure until 1887 when Sir David Bruce - a Scottish physician reported numerous small coccal organisms in stained sections of spleen from a fatally infected soldier and isolated and identified organism in culture from spleen tissue of four other British soldiers stationed at Malta. Human Brucellosis is not considered a contagious disease and people become infected by contact with fluids from infected animals (sheep, cattle or pigs) or derived food products like unpasteurized milk and cheese. Brucellosis is also considered an occupational disease because of a higher incidence in people working with animals (slaughterhouse cases). The real worldwide incidence of Brucellosis is unknown because there is a low level of surveillance and reporting in brucella-endemic areas.

Case History
42 year old male non diabetic, non hypertensive was admitted with complaints of fever for 3 weeks, retrosternal burning on and off for 3-4 weeks and weight loss of about 15 kgs in last 10 months. Patient was apparently well 3 weeks back when he started having fever with chills not associated with rigors or headache, which was initially up to 101°F and for last 4-5 days came up to 104°F. Fever was continuous and he also had cough on and off for last 10 months. He also complained of weight loss of 15 kgs in last 10 months with decreased appetite. Patient was admitted earlier in a hospital in October with complaints of fever on/off for 8 months. He was evaluated that time and found to have Mantoux 10 x 10 mm and Serum Quantiferon gold was positive. His CT Chest and abdomen at that time showed mild splenomegaly with small hypodense splenic SOL likely haemangioma. No other significant intra thoracic or intra abdominal abnormality was noted. An NCCT Para nasal sinus was done which revealed mild right frontal and maxillary mucosal disease with right-sided DNS and bony nasal spur. Patient was afebrile during the previous hospitalization. Patient was a resident of a village in Nainital district and had daily contact with farm animals and cow dung as he used to pass through the farmlands while going to work. His routine hematological parameters showed Hemoglobin of 13.5 gm/dl, total leucocyte count 6500/cumm, platelets 3.5 lakhs/cumm lymphocytosis was present in peripheral smear. ESR was 65 mm in 1st hr. Biochemical parameters showed creatinine of 1.0 mg/dl, total protein/albumin 6.5 gm/dl/3.5 gm/dl, total bilirubin 0.8/0.2 mg/dl, SGOT 35 IU, SGPT 45 IU, S. Alkaline Phosphatase 145 IU, gamma GT 70 IU. Chest X-Ray was normal. Blood culture was initially negative. Malarial parasite serology was negative. Urine routine was normal. HIV was negative. c-ANCA, p-ANCA were negative. C3/C4 was normal. Echocardiography was normal. Patient was treated with IV antibiotics (Ceftriaxone), antipyretics, cough suppressants and other symptomatic and supportive treatment. But patients fever did not settle. In view of long standing fever of 10 months, a bone marrow aspiration, biopsys, C/S, gene probe for TB and AFB staining was done. Bone marrow aspiration was suggestive of lymphocytosis. Bone marrow biopsy was suggestive of involvement by a granulomatous lesion. Gene probes for TB and BM AFB staining was negative. A CECT abdomen was repeated after gap of 2 months, which revealed few peri-portal and peri-pancreatic lymph nodes (upto 1 cm size) with hepatosplenomegaly and the splenic SOL was not visualized this time. Meanwhile blood culture and bone marrow culture showed a delayed growth of Brucella melitensis after 4 days of culture. Patient’s ceftriaxone was stopped and started on doxycycline 100mg twice daily for 6 weeks and streptomycin 1 gm daily intramuscularly for 2 weeks. Patients fever settled and on 6 months of follow up he is asymptomatic.

Discussion
Worldwide, brucellosis remains a major source of disease in humans and domesticated animals. The disease is endemic especially in countries of the Mediterranean basin, the Arabian Gulf, the Indian subcontinent and parts of Mexico and Central and South America. Human brucellosis is found to have significant presence in rural/nomadic communities where people live in close association with animals. Worldwide, reported incidence of human brucellosis in endemic disease areas varies widely, from <0.01 to >200 per 100,000 population. The true incidence of human brucellosis however, is unknown for most countries including India. It has been estimated that the true incidence may be 25 times higher than the reported incidence due to misdiagnosis and underreporting. The occurrence of...
brucellosis in India was first established early in the previous century and since then has been reported from almost all states. Several publications indicate that human brucellosis can be a fairly common disease in India. Mathur reported 8.5% seroprevalence of brucellosis among dairy personnel in contact with infected animals with the isolation of Brucella strains from seven cases of human brucellosis. In Gujarat, 8.5% prevalence of Brucella agglutinins was recorded in human cases. In Haryana, 34% prevalence of human brucellosis was recorded among veterinarians, attendants and compounders in contact with animals. Since uncharacterized fever is the only manifestation in a large number of patients some workers screen pyrexia of unknown origin (PUO) cases for evidence of brucellosis. Handa and coworkers identified four (3.3%) cases with acute brucellosis in a group of 121 patients with PUO.

Human brucellosis is known for presenting with protean manifestations. However, the most common presenting symptom is fever. In a large study from Rajasthan patients of brucellosis presented with a wide spectrum of clinical manifestations. Out of 175 cases, 155 were from rural area. Analysis of risk factors revealed history of raw milk ingestion (86.86%), occupational contact with animals (81.14%), handling of infected material (62.28%), household contact (16%) and 2 patients were veterinarian. Joint pain (83.43%) and fever (77.71%) were the commonest presenting feature. Sacroiliac joint was most commonly involved (46.86%). 31 cases had involvement of multiple joints. Other mode of presentation were neurobrucellosis (18.86%), manifested as polyradiculoneuropathy, myeloradiculopathy, meningoencephalopathy and polyradiculomyeloneuroencephalopathy; predominant pulmonary involvement (4.0%) presented as bronchitis, pneumonia and pleural effusion; epididymoorchitis, infective endocarditis, nephritic syndrome and recurrent abortion. All patients responded well to the treatment. Some authors consider malodorous perspiration as almost pathognomonic. Malodorous perspiration is usually manifested as an acute (< 2 months) or subacute (2-12 months) febrile illness, which may persist and progress to a chronically (> 1 year) incapacitating disease with severe complications. Persons infected with Brucella spp. usually have signs and symptoms consistent with an influenza like or septicaemic illness, often with insidious onset. The symptoms and clinical signs most commonly reported are fever, fatigue, malaise, chills, sweats, headaches, myalgia, arthralgia and weight loss. Some cases have presented with only joint pain, low back ache, involuntary movements of limbs, burning feet, or ischemic heart attacks. Typically, no or few objective signs are apparent that specifically point to brucellosis. Enlargement of the liver, spleen and/or lymph nodes may occur as may other signs referable to almost any other organ system. These febrile patients may be referred to as patients with pyrexia of unknown origin or the symptoms and signs are confused with those of other diseases such as enteric fever, malaria, rheumatic fever, tuberculosis, cholecystitis, thrombophlebitis, fungal infection, autoimmune disease and tumours. Thus to an unaware physician, the clinical diagnosis becomes a challenging one. The acute form of human brucellosis is characterized by an undulating fever, in addition to the signs and symptoms mentioned. The temperature remains normal during the early part of the day and rises during the evening. Lack of appropriate therapy during the acute phase may result in localization of bacteria in various tissues and lead to sub acute or chronic disease that can have serious clinical manifestations. Brucellosis in humans occurs in all age groups. Human brucellosis is known for complications. Complications can be very diverse depending on the specific site of infection. Osteoarticular, genitourinary, gastrointestinal, nervous, cardiovascular, skin and mucous membranes and respiratory complications are observed. The reports of unusual manifestations with atypical lesions in brucellosis are on the rise due to availability of diagnostic facilities and awareness. In conclusion, it should be noted that brucellosis may affect essentially any organ - a fact that reinforces the importance of including brucellosis in the differential diagnosis even if clinical features are not entirely compatible, especially in endemic areas. In all cases it is important that the patient completes the full course of therapy because the risk of incomplete recovery and relapse is otherwise increased considerably. The treatment recommended by the World Health Organization for acute brucellosis in adults is Rifampicin 600 to 900 mg and doxycycline100 mg twice daily for a minimum of six weeks. Some still claim that the long-established combination of intramuscular streptomycin (1 g/day for two-three weeks) with an oral tetracycline (2 g/day for six weeks) gives fewer relapses. Trimethoprim-sulfamethoxazole is a popular compound in many areas, usually used in triple regimens. Quinolones are an alternative. Various combinations that incorporate ciprofloxacin and ofloxacin have been tried clinically, yielding similar efficacy to that of the classic regimens. Although the results are encouraging, additional experience is needed in order to determine the role of fluoroquinolones in the treatment of brucellosis. Relapses occur at a rate of about 10% and are often milder in severity than the initial disease and can be treated with a repeated course of the usual antibiotic regimens. Most complications of brucellosis can be adequately treated with standard regimens. Treatment of some complications like spondylitis, osteomyelitis, neurobrucellosis and endocarditis also require combination therapy but longer courses. Human brucellosis can be treated with a combination of antibiotics but is very difficult to diagnose and requires laboratory testing for confirmation. Only a few recent studies have addressed the prevalence and importance of brucellosis as a human disease problem in India. The disease may be overlooked and misdiagnosed because of the difficult diagnosis and the absence and lack of experience with the laboratory testing. Alertness of medical staff is needed to recognize and diagnose the disease. Awareness of risk groups is needed to take appropriate preventive measures and to accept control measures.

References
A 46 years male resident of Gujarat was admitted for fever, cough with expectoration, and breathlessness for 15 days. His past medical history included end-stage renal disease (ESRD) from hypertension. Prior to hospitalization he was treated in private hospital with intravenous antibiotics and anti-fungal for 7 days, however his clinical condition deteriorated. On admission, his temperature was 38°C; respiratory rate was 30/min, and arterial oxygen saturation on room air was 86%. His hemoglobin was 7.8 gram%, WBC count 2.6 x 10^4 /cmm, and platelet count 4 x 10^4 /cmm. His S. creatinine (SCr) was 6 mg %. X-ray chest showed bilateral pneumonia. Subsequently he required invasive ventilation. Real-time reverse-transcriptase–polymerase-chain-reaction assay (RT-PCR) from nasal and pharyngeal swab showed H1N1. Positive contact history matched with RT-PCR confirmed diagnosis of H1N1 during prior hospitalization. Oral oseltamivir with a renally adjusted dosage was begun. He was shifted to isolation ward. Patient died on day 5 of admission. Post-exposure chemoprophylaxis with oseltamivir was given to close contact.

Renal Transplant Recipient

A 40 year female resident of Gujarat with history of chronic glomerulonephritis-ESRD on hemodialysis for 4 months was admitted for renal transplant with husband as donor. She had past history of pulmonary tuberculosis and hypertension. She had 2 children and received 2 units of red cells for anemia. Due to pre-sensitization she was subjected to desensitization protocol of bortezomib (1.3mg/m^2 × 6 doses), six therapeutic plasmapheresis (35ml/kg), intravenous immunoglobulin (5 gram × six doses) and mycophenolate mofetil (MMF) (1.5gram daily x 4 weeks) She received intra-operative induction therapy with methylprednisolone, 500 mg and anti-thymocyte globulin (ATG) (1.5 mg/kg). She had immediate good allograft function with 14 liter urine output and her S. Cr was 0.9mg%. For maintenance immunosuppression, she received prednisolone (20 mg daily), tacrolimus (0.08 mg/kg/day) and MMF (1.5gram/day). Her immediate post- transplant period was complicated by close contact with patient of pneumonia for 3 days which later was diagnosed to have RT-PCR proven H1N1. She had no history of H1N1 vaccination in pretransplant period. In view of significant exposure to H1N1 infection and her immunosuppression including desensitization protocol, oseltamivir prophylaxis (75 mg once daily) was administered for 10 days. H1N1 vaccine was not available to our patient. Immunosuppressive therapy was not reduced. The trough tacrolimus level before and after oseltamivir prophylaxis, were 11.3 and 11.1 ng/ml (reference range: 4-20 ng/ml). The remainder of her posttransplant course was uneventful; she was discharged on 12th posttransplant day with no signs/symptoms of H1N1 and with continued excellent graft function (SCr 0.8 mg %). Throughout her course, she did not manifest any signs/symptoms of influenza like illness/ fever/ cough/ sore throat/headache / running nose. She did not develop any adverse effects from oseltamivir prophylaxis including any drug interaction with immunosuppressive therapy.

Discussion

While solid organ transplant recipients under immunosuppressive therapy may be at higher risk for H1N1 complications when exposed to close contacts, our report suggested a benefit...