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Brucellosis and tuberculosis: Clinical overlap and pitfalls

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ABSTRACT

Objective: To identify characteristic features of tuberculosis in patients with culture proven brucellosis. **Methods:** A retrospective analysis was performed on patients diagnosed with culture proven brucellosis between January and December 2011, based on review of their medical records. Patients with demonstrable co-infection with tuberculosis were excluded. Clinical features, laboratory parameters and tissue histopathology reports where available were noted. **Results:** Thirty-two patients with brucellosis were included in the study. Twenty-one (65.63%) patients had chronic fever, thirteen (40.63%) had a productive cough, while significant weight loss, evening rise of temperature and night sweats were reported by eight (25.00%), eleven (34.38%) and five (15.63%) patients respectively. Nine (28.13%) patients had at least three of these symptoms. Lymphadenopathy, hepatomegaly and splenomegaly were noted on examination in seven (21.88%), fifteen (46.88%) and twelve (37.50%) patients respectively. Eight (25.00%) patients had hepato-splenomegaly, of these only two had associated significant lymphadenopathy. Respiratory examination was normal in all patients. Elevated ESR greater than 50 mm/hr was seen in eight (25.00%), it was greater than 100 mm/hr in five (15.63%) patients. Hypergammaglobulinemia was seen in eight (25.00%) cases. Bone marrow biopsy showed non-caseating granulomas in three (9.38%) cases, lymph node biopsy showed granulomas in one case. Overall, three (9.38%) patients had known risk factors for tuberculosis, while six (18.75%) had risk factors for brucellosis. **Conclusions:** There is a clear overlap between brucellosis and tuberculosis both in terms of clinical presentation and laboratory parameters. It is essential to carefully rule out tuberculosis in all cases of suspected or proven brucellosis before initiating antimicrobial therapy, in order to forestall development of drug-resistant tuberculosis.

1. Introduction

Brucellosis and tuberculosis are two chronic granulomatous infectious diseases that are ubiquitous in the developing world. Brucellosis is now considered to be the commonest zoonosis in the world with a global annual incidence of more than a half million[1], and is specifically endemic to developing countries[2-3]. It is produced by infection with any of several members of the *Brucella* family including *Brucella melitensis*, *Brucella abortus* and *Brucella suis*. Human brucellosis results from ingestion or inhalation of the organism, or inoculation through skin abrasions. Once in the bloodstream, the organism replicates within the reticuloendothelial system. Being facultatively intracellular, the organism can survive and multiply within phagocytic cells, evading immune-mediated clearance[1]. Persistent infection and resultant activation of the immune system, results in a state of chronic inflammation, characterized by hypergammaglobulinemia and elevated erythrocyte sedimentation rate. Clinical correlates of reticuloendothelial activity include hepato-splenomegaly and lymphadenopathy. Histopathology of affected tissues including lymph nodes and bone marrow frequently reveals non-caseating granulomas[4]. These laboratory and histologic features of chronic brucellosis share similarity

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with tuberculosis-another infectious disease endemic to many developing countries.

This study was therefore designed to identify characteristic clinical, laboratory and histopathologic features of tuberculosis in patients with culture proven brucellosis, in order to assess the likelihood of misdiagnosis as tuberculosis.

2. Materials and methods

2.1. Study settings

Kasturba Medical College, Manipal is a major tertiary care hospital in Southwestern India. It has a catchment area corresponding to the district of Udupi in which it is situated, and the neighbouring districts of Uttara Kannada and Dakshina Kannada, with a combined population approximately 4.36 million individuals.

A retrospective analysis was performed on patients diagnosed with culture proven brucellosis between January and December 2011, based on review of their medical records. Patients with demonstrable co-infection with tuberculosis in the form of positive identification of acid fast bacilli in sputum or tissue samples and/or isolation of *Mycobacteria tuberculosis* in culture from any sample, were excluded. Clinical features, laboratory parameters and tissue histopathology reports where available were noted. Specifically, features suggestive of tuberculosis were looked for. Among clinical features, a history of prolonged fever (>4 weeks), chronic productive cough, significant weight loss (>10% of baseline body weight prior to onset of illness), evening rise of temperature, and night sweats were noted. Risk factors for tuberculosis including a history of exposure to a known case of tuberculosis, and any form of immunosuppression including HIV infection, chronic kidney disease, and diabetes mellitus were identified. Risk factors for brucellosis such as occupational exposure were noted. Clinical stigmata of tuberculosis including respiratory disease, lymphadenopathy, and hepato-splenomegaly were recorded. Laboratory markers of tubercular disease including elevated ESR, hypergammaglobulinemia, and tissue evidence of granulomatous disease were also looked for.

2.2. Statistical analysis

All data was analysed using SPSS Statistics version 17.0 (Chicago IL, USA). Continuous variables were presented as mean±standard deviation (SD).

3. Results

Thirty-two patients with brucellosis were included in the study. Mean age at presentation was (34.28±13.52) years. Twenty-four of the patients were male, yielding a male:female ratio of 3:1.

Chronic fever was (>4 weeks) seen in 21 (65.63%) patients, evening rise of temperature in 11 cases (34.38%), while 13 (40.63%) had a productive cough. Significant weight loss was seen in 8 cases (25%), night sweat in 5 cases (15.63%). Other symptoms suggestive of tubercular disease were also noted. Of the 32 patients, nine (28.13%) reported at least three of these symptoms. Two patients had four symptoms, while one patient had all five symptoms. Six patients denied any of these symptoms. Careful search for risk factors showed that three (9.38%) patients had known risk factors for tuberculosis, while six (18.75%) had risk factors for brucellosis. The majority of patients denied risk factors for both tuberculosis and brucellosis.

Clinical examination revealed significant lymphadenopathy in seven (21.88%) patients. Hepatomegaly and splenomegaly were observed in fifteen (46.88%) and twelve (37.50%) patients respectively. Eight (25.00%) patients had hepato-splenomegaly, of these only two had associated significant lymphadenopathy. Interestingly respiratory examination was normal in all patients, including those complaining of cough. Review of laboratory parameters showed an ESR greater than 50 mm/hr in eight (25.00%) patients; of these patients, it was greater than 100 mm/hr in five (15.63%). Hypergammaglobulinemia was seen in eight (25.00%) cases. Bone marrow biopsy showed non-caseating granulomas in three (9.38%) cases, lymph node biopsy showed granulomas in one case. Chest radiograms were normal in all patients.

All patients received standard chemotherapy with oral doxycycline and rifampicin. Twelve patients also received initial therapy with parenteral streptomycin.

4. Discussion

Diagnosis of brucellosis requires isolation in culture of the organism from blood[5] and/or bone marrow[6], or serologic evidence of infection by the standard tube agglutination[7] or enzyme linked immunosorbent assay[8]. Needless to say, these diagnostic techniques are often unavailable in many areas of developing countries, resulting in significant underreporting of cases[9]. It is quite reasonable to surmise that a proportion of these patients might be misdiagnosed as tuberculosis based on similarities in presentation and basic laboratory parameters. Fortunately, several anti-tubercular drugs including rifampicin and streptomycin also possess excellent activity against Brucella species[10]. However, the opposite case is equally plausible wherein a patient diagnosed with brucellosis may have underlying tuberculosis. Treatment with standard therapy in such cases entails exposure of the patient to inadequate doses and duration of anti-tubercular drugs, likely increasing the chance of development of drug-resistant tuberculosis.

Drug resistance in tuberculosis is rapidly becoming a global problem, and now threatens to overcome progress achieved in tuberculosis control. Estimated global annual incidence of multidrug resistant (MDR) tuberculosis is approximately 440 000[11]. Of these cases, nearly half are present in India and China[11]. The direct economic fallout of MDR tuberculosis is a rise in healthcare costs-resulting from drug sensitivity testing, and prolonged therapy with

expensive second-line drugs[12].

The principal driving force behind the emergence of these MDR strains is now known to selective antibiotic pressure[13] by inadequate or inappropriate drug therapy, promoting survival of mutant organisms that are resistant to first-line therapy[14,15]. In such a situation, the importance of rational use of anti-tubercular drugs cannot be over-emphasized. While several studies have demonstrated the clinical overlap between tuberculosis and other infectious diseases such as melioidosis[16] and histoplasmosis[17-19], it is pertinent to note that treatment for these conditions is entirely different, in sharp contrast to brucellosis. Chemotherapy for brucellosis includes rifampicin and streptomycin-two first-line antitubercular drugs, prescribed over a period of six weeks. The WHO oral regimen consists of 200 mg doxycycline and 600 mg rifampicin daily for at least 6 weeks[10]; the alternate oral/parenteral regimen replaces rifampicin with 15 mg/kg parenteral streptomycin daily for the first 14-21 days of treatment[20,21]. Uncontrolled prescription of these drugs without conclusively ruling out underlying tuberculosis can be disastrous for the patient. Given the large geographical overlap and high prevalence of both these diseases, such a scenario is certainly feasible and is a potentially unrecognized contributor to the development of MDR tuberculosis. Our study demonstrates the remarkable degree of overlap between chronic brucellosis and tuberculosis, both in terms of clinical presentation and basic laboratory parameters. The relatively low proportion of patients with risk factors emphasizes the unreliability of these factors in making a diagnostic decision.

In summary, beyond the obvious diagnostic dilemmas that such mimicry can pose, there are also major implications for treatment in the similarity between brucellosis and tuberculosis. Physicians should exercise extreme care in ruling out co-existent tuberculosis before initiating therapy in all patients with proven brucellosis. Empirical antibiotic therapy for suspected brucellosis is best avoided altogether. Risk factors for brucellosis and tuberculosis are poor indicators and should not be relied upon to make the distinction, especially in developing countries with high prevalence of both diseases.

Conflict of interest statement

We declare that we have no conflict of interest.

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