Seronegative Brucella melitensis Infection with Bacteremia in a Diabetic Patient
F Albayrak, A Azap, O Memiko?lu, S Birengel, H Kurt

Citation

Abstract
Immunity to Brucella spp. depends on antigen-specific T cell-mediated activation of macrophages. The course of infections in patients with diabetes mellitus (DM) is more severe and complicated. The possible cause is defect in immunity. Since the DM affects both the cellular and humoral immunity, patients with DM may have limited primary antibody response to T-cell dependent antigens such as Brucella bacteria, which makes the diagnosis more difficult. So patients suspected of having brucellosis should be evaluated by blood cultures besides Brucella Standard Agglutination Test (SAT), rose Bengal test and Brucella ELISA IgG and IgM tests by physicians especially in areas where the disease is endemic.

INTRODUCTION
The members of the genus Brucella are gram-negative, facultative intracellular cocobacilli that cause brucellosis in many animal species and humans. The protective immune response against Brucella bacteria involves both humoral and cell-mediated immunity (1). Acquired immunity against intracellular bacteria is T cell dependent which means T cells play the major role in protection against these organisms, but bacterial antigens recognized by T cells have been studied less than bacterial antigens recognized by B cells (2,3).

Cellular immune responses are a critical part of the host's defense against intracellular bacterial infections. Immunity against Brucella spp. depends on antigen-specific T cell-mediated activation of macrophages, which are the major effectors of cell-mediated killing of this organism (1). In addition to the central role of the macrophage in Brucella infection, others cells of the immune system are influenced by the interactions between bacteria and host. These cells can counteract the intramacrophagic development of the bacteria and finally influence the further development of the host defense (1,3).

The presumptive diagnosis of Brucellosis is based on a high or rising antibody titer measured by the Brucella Standard Agglutination Test (SAT). These tests do not discriminate between the immunoglobulin classes (IgG and IgM). Diagnostic value of SAT with Brucella Enzyme Linked Immunosorbent Assay (ELISA) IgG and IgM tests in patients with Brucella bacteremia have similar sensitivity (1).

CASE REPORT
A 49-year-old female patient admitted to our department with complaints of fever, malaise, nausea/vomiting and arthralgia. One week history of fever reaching to 39 ° C and night sweats together with arthralgia of the knee, ankle and wrist was elicited from the patient. She had diabetes for 10 years with poor glycemic control.

Physical examination revealed an axillary temperature of 37.5 ° C, respiratory rate of 15/min, a blood pressure of 130/80 mmHg. The physical examination of the organ systems were completely normal. Complete blood count showed 7200 white blood cells with 55 % neutrophils and 33 % lymphocyte, and erythrocyte sedimentation rate was 18 mm/hour. Biochemical tests except for blood glucose (216mg/dL) and urinalysis were normal.

Two consecutive blood cultures were drawn during periods of fever and monitored with BACTEC 9120 blood culture system. Since brucellosis is an endemic disease in our country, rose Bengal and Standart Agglutination Tests (SAT) were done and the results were negative. On the 3 rd day of admission, blood cultures were positive for a gram-negative cocobacilli. The biochemical tests of the isolated bacteria were positive for oxidase, catalase and urease.

Patient was started a combination therapy of doxycycline 200mg/d and rifampin 600 mg/day. The isolated bacteria
was serotyped at the Pendik Research Institute in Istanbul as Brucella melitensis type III.

After the first week of admission, SAT with 2-mercaptoethanol, Brucella Coombs test and Brucella Enzyme Linked Immunosorbent Assay (ELISA) IgG and IgM tests were done, with results being negative. The symptoms of patient disappeared at the end of the 1st week and the treatment continued for 6 weeks. On follow up, the patient's sera were tested during the 6th week, the 3rd and the 6th month of the disease, with the results being negative for SAT again.

DISCUSSION

Pathogens have developed different strategies to survive and multiply within their host. Among them is the ability to affect the expression of cytokines which is necessary for a normal protective function of the immune response. To establish themselves and cause chronic disease in humans and animals, Brucella spp. invade and proliferate within monocytic phagocytes (1).

Infections activate the immune system, leading to a series of metabolic changes which place the organism at a disadvantage and contribute to its elimination. The study of the actions of cytokines; tumour necrosing factor alpha (TNF-alpha) and interleukin-6 (IL-6), classically implicated in inflammatory processes and in fighting infection, has revealed numerous metabolic effects (2).

It is well known that infections in patients with diabetes mellitus are more severe, although there is controversy for increased susceptibility to them. Non-specific immune response mechanisms could be related to defense and/or susceptibility to pathogens (3). The course of the infections is also more complicated in this patient group. One of the possible causes of this increased prevalence of infections is defects in immunity. Different disturbances (low complement factor 4, decreased cytokine response after stimulation) in humoral natural immunity have been described in diabetic patients. However, the clinical relevance of these findings is not clear yet. Concerning cellular natural immunity most studies show decreased functions (chemotaxis, phagocytosis, killing) of diabetic monocytes/macrophages compared to cells of controls (4). Since the DM affects both the cellular and humoral immunity primary antibody response to T-cell dependent antigens and also the T-cell response to primary protein antigens are reduced in patients with diabetes.

Some authors report that antibodies to cytoplasmic proteins (CP) of Brucella have been shown to be useful for the diagnosis of human brucellosis; however, some early-diagnosed patients lack such an antibody response while having high titers of antibodies to lipopolysaccharide (LPS) (10). Especially patients with acute infections respond to CP whereas chronically infected patients do not (10,11).

In our case antibodies to LPS was lacking both at the beginning and end of the disease. As described above, patients with underlying diseases interrupting immune system such as DM, may have limited ability to produce antibody against pathogen organisms, unlike immunocompetent patients. This makes the diagnosis more difficult. So we conclude that, patients suspected to have brucellosis should also be evaluated by blood cultures whether the patient has fever or not, besides SAT and Brucella ELISA IgM and IgG by physicians especially in areas where the disease is endemic. Other methods such as antibodies to cytoplasmic proteins (CP) of Brucella, immunocapture technique which has been applied to the diagnosis of ovine brucellosis under experimental conditions should also be thought for diagnosis of human brucellosis (11,12).

CORRESPONDENCE TO

Fahrettin ALBAYRAK M.D. Specialist, Pamukkale University Medical Faculty Infectious Diseases Department, Denizli/Turkey Adress: Mavi Hastane-Kınklı Kampusu-Kınklı-Denizli Zip Code:20020 e-mail: falbayrak@yahoo.com Tel:+90-312-4786354

References

Author Information

Fahrettin Albayrak, M.D.
Specialist, Infectious Diseases Department, Pamukkale University Medical Faculty

Alpay Azap, M.D.
Specialist, Clinical Bacteriology and Infectious Diseases Department, Ankara University Medical Faculty

Osman Memiko?lu, M.D.
Specialist, Clinical Bacteriology and Infectious Diseases Department, Ankara University Medical Faculty

Serhat Birengel, M.D.
Associate Professor, Clinical Bacteriology and Infectious Diseases Department, Ankara University Medical Faculty

Halil Kurt, M.D.
Professor, Clinical Bacteriology and Infectious Diseases Department, Ankara University Medical Faculty