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PHOTO OUIZ

A 40 years old woman with fever and pancytopenia

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CASE SUMMARY

A 40 years old woman residing in a rural area, referred with chief complaint of fever and generalized body pain since 4 months ago which was aggravated during the recent month. She had history of intermittent fever, mostly at nights. She had not traveled. On admission, she was depressed and pale in appearance with stable vital signs. On physical examination, spleen was palpable 5 cm below costal margins and spanned about 15 cm in midclavicular line. She had no adenopathy or rash. Laboratory studies revealed leukopenia (WBC =2100/ml), anemia (hemoglobin =10.6gr/dl), thrombocytopenia (platelet =100,000/ml), aspartate aminotransferase (AST) =90U/l and alanine aminotransferase (ALT) =80U/l. Peripheral blood smear for malaria and borellia, serologic tests for brucellosis (Wright and Coombs Wright) and blood cultures were all negative after 3 attempts. Chest radiography and abdominal CT scan revealed no pathology except for splenomegaly. Bone marrow aspiration was negative for malignancy, leishman body and acid fast staining for mycobacteria, but biopsy revealed granulomatous reaction with epitheloid cells and mononuclear infiltration (Fig.1). Liver biopsy showed granulomatous reaction with mononuclear and some neutrophil infiltration (Fig.2). *What is the diagnosis?*

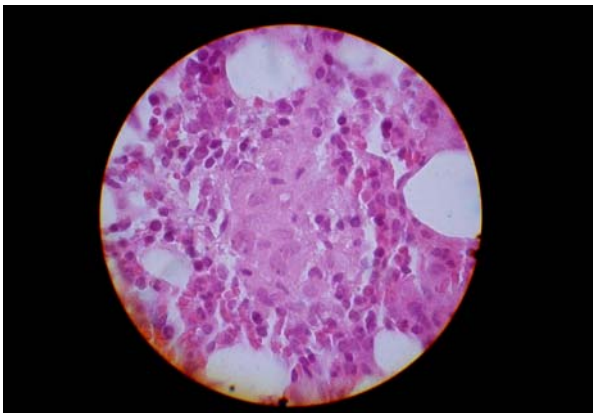

Figure 1. *Granulomatous reaction with epitheloid cells and mononuclear infiltration in bone marrow biopsy*

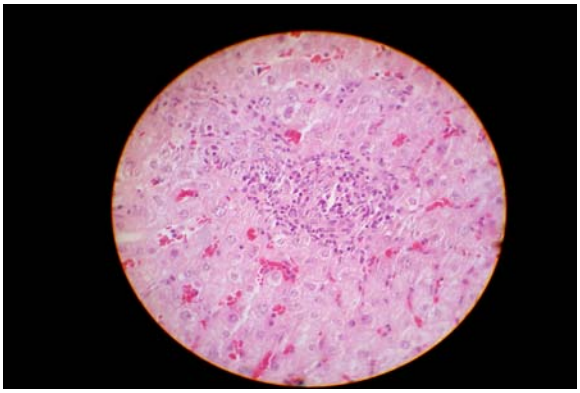

Figure 2. *Liver biopsy showed granulomatous reaction with mononuclear and some neutrophile infiltration*

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ANSWER TO PHOTO QUIZ

Diagnosis: Brucellosis

Result of bone marrow culture in Castaneda medium revealed gram negative coccobacilli on the 15th day of culturing that was identified as brucella abortus (Fig. 3).

Brucellosis is a major zoonotic disease that remains endemic in many developing countries and in rural areas of many developed countries around the world (1,2). Brucellosis, like tuberculosis, is a chronic granulomatous infection caused by intracellular bacteria and requires combined, protracted antibiotic treatment. The disease causes much clinical morbidity as well as a considerable loss of productivity in animal husbandry in the developing world. In this era of international tourism, brucellosis has become a common imported disease in the developed world (3). It is commonly implicated in the everyday differential diagnosis in various clinical settings, because the peculiar presentations and complications of the infection are not rare (4). Transmission is achieved through direct contact with contaminated animals, ingestion of infected dairy products, and inhalation of infectious aerosol particles. The last means of transmission is not only the route by which brucellae achieve direct contact with the respiratory system, but it is a route that has potential for use in biological warfare (5).

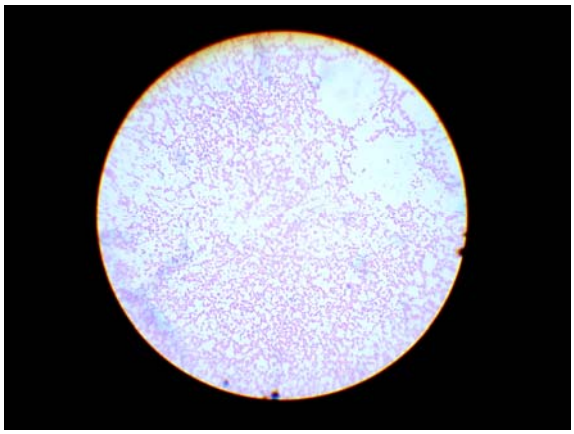

Figure 3. *Bone marrow culture revealed gram negative coccobacilli on day 15*

Because the liver is the largest organ of the reticuloendothelial system, it is probably always involved in brucellosis. However, liver function tests are usually only slightly elevated. The spectrum of pathologic findings in brucellosis hepatitis is varied (6). B.abortus infection is characterized with granuloma that is indistinguishable from sarcoidosis (7). Hepatic lesions resolve with antimicrobial therapy, and in the absence of other causes (e.g., hepatitis C or alcohol abuse), cirrhosis does not occur despite the severity of the inflammation (8).

The blood count is often characterized by mild leukopenia and relative lymphocytosis, along with mild anemia and thrombocytopenia. Pancytopenia in brucellosis is multifactorial and is attributed to hypersplenism and bone marrow involvement. Rarely, marked pancytopenia or isolated deficits can be attributed to diffuse intravascular coagulation, hemophagocytosis, or immunologically mediated cellular destruction (5). Granulomas are found in the bone marrow in up to 75% of cases, but they are small and indistinct (6). The erythrocyte sedimentation rate is variable and of little diagnostic value (9).

The absolute diagnosis of brucellosis requires isolation of the bacterium from blood or tissue samples. The sensitivity of blood culture varies, depending on individual laboratory practices and how actively the obtaining of cultures is pursued. The percentage of cases with positive cultures ranges from 15 to 70 percent (10).

When brucellosis is suspected, the laboratory should be alerted to maintain cultures for a minimum of 4 weeks(12). Brucellae are cultured in standard biphasic (solid and liquid) mode or with the Castaneda bottle, which incorporates both solid and liquid mediums in the same container. Automated systems are also reliable in isolating brucella (11). Cultures of bone marrow have a higher yield than blood (12). Bone marrow cultures are considered the gold standard for the diagnosis of brucellosis, since the relatively high

concentration of brucella in the reticuloendothelial system makes it easier to detect the organism (13).

There are two broad categories of serologic methods for diagnosing brucellosis: those based on antibody production against lipopolysaccharide and those based on antibody production against other bacterial antigens. Developed by Bruce, the serum agglutination test remains the most popular diagnostic tool for brucellosis. Titers above 1:160 are considered diagnostic in conjunction with a compatible clinical presentation. However, in areas of endemic disease, using a titer of 1:320 as diagnostic may be more specific. Seroconversion and evolution of the titers can also be used in diagnosis. Lack of seroconversion can be attributed to the performance of tests early in the course of infection, the presence of blocking antibodies, or the so-called "prozone" phenomenon (i.e., the inhibition of agglutination at low dilutions due to an excess of antibodies or to nonspecific serum factors) (14).

Treatment of human brucellosis should involve antibiotics that can penetrate macrophages and can act in the acidic intracellular environment. There is a general need for combined treatment, since all monotherapies are characterized by unacceptably high relapse rates.

In 1986, the World Health Organization issued guidelines for the treatment of human brucellosis. The guidelines discuss two regimens, both using doxycycline for a period of six weeks, in combination with either streptomycin for two to three weeks or rifampin for six weeks. Both combinations are the most popular treatments worldwide, although they are not used universally. The streptomycin-containing regimen is slightly more efficacious in preventing relapse (15).

The patient was treated with doxycycline and rifampicin for 6 weeks. She was afebrile after 2 weeks and resolved leukopenia and thrombocytopenia after 4 weeks.

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