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Brucella-induced Thrombocytopenia and Bleeding

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Abstract

Mild anemia and leukopenia are the most common hematologic problems of acute brucellosis. Mild thrombocytopenia also occurs, but severe cases are uncommon. Thrombocytopenia occurs because of bone marrow suppression, hypersplenism, hemophagocytosis, and immunologic destruction of the cells or disseminated intravascular coagulation. In endemic areas, hemorrhagic fevers, hematologic malignancies, as well as idiopathic thrombocytopenic purpura should be considered as differential diagnoses for complicated brucellosis. Thrombocytopenia and bleeding can be improved with antibiotic and hematologic supportive therapy whereas in severe cases corticosteroid therapy or splenectomy might be necessary.

Keywords: Brucella, thrombocytopenia, fever, hemorrhage

1. Introduction

Although brucellosis is a treatable and non-severe disease, 5–10% of patients experience some complications [1]. Brucella plays an important role in infectious diseases, and can mimic many other infectious and non-infectious diseases. This mimicry can result in delayed diagnosis and increased mortality and morbidity. Almost all body systems can be affected by brucellosis, including the hematological system.

The most common hematological finding in brucellosis is an unchanged hemogram, including normal counts of platelets, white blood cells, and hemoglobin [2]. Hematological problems may occur and are most common in children with brucella infection, but sometimes occur in adults as well. Several blood disorders have been reported in brucellosis, including hemolytic

anemia [3], thrombocytopenia, leukopenia [4], leukocytosis [5], thrombocytosis [6], and pancytopenia [7]. Mild anemia and leukopenia are the most common complications of acute infection. Mild thrombocytopenia also occurs in about 1–26% of the patients, while severe cases are uncommon [4].

Isolated thrombocytopenia or pancytopenia has been rarely reported. Severe thrombocytopenia with pancytopenia imitates hematologic diseases (Figure 1). Thrombocytopenia occurs less than leukopenia in brucellosis. We and others have several published [8–10] and unpublished papers regarding confirmed brucellosis cases presenting with severe hemorrhagic fever mimicking Crimean-Congo Hemorrhagic Fever (CCHF). These patients are usually isolated before an established diagnosis is reached.

Mild thrombocytopenia is more common than the severe form and the incidence of splenomegaly in thrombocytopenic cases is higher than that reported for uncomplicated brucellosis [11]. Thrombocytopenic purpura and microangiopathy may also occur in brucellosis [12, 13]. The latter event may be associated with thrombocytopenia, bleeding, hemolytic anemia, and impaired consciousness. Disseminated intravascular coagulation (DIC) is rarely seen [14]. DIC may occur in the patients suffering from gram-negative sepsis. Bacterial endotoxins activate the coagulation cascade. Microrhrombi are deposited in the wall of the vasculature, resulting in thrombosis, bleeding, and Microangiopathic Hemolytic Anemia (MAHA). DIC and/or MAHA are rarely reported in association with brucellar endocarditis with the clinical presentation of mild disease to severe bleeding, thrombosis, and death [2].

Hence, brucellosis must be considered in the differential diagnosis of all those conditions leading to diverse hematologic disorders including pancytopenia, hemolytic anemia, leukopenia, thrombocytopenia, and disseminated intravascular coagulation in endemic areas [15, 16].



Figure 1. Ecchymosis of the lower limbs in a patient with brucella-induced hemophagocytosis.

The key point in the evaluation of thrombocytopenia is to prepare a peripheral blood smear to assess the morphology of the blood cells and to exclude pseudo-thrombocytopenia, especially in patients with an unexplained low platelet count. The latter condition is attributed to the use of certain anti-coagulants (such as ethylenediamine tetra-acetic) and subsequent platelet agglutination [17].

Although bone marrow smear and culture plays an important role in detecting infectious causes of thrombocytopenia, it is possible to find the etiology of thrombocytopenia with less invasive procedures such as blood smear and culture. In many cases, thrombocytopenia will disappear after antibiotic therapy within a few days. Therefore, in suspected infectious induced thrombocytopenia, there is often no need for bone marrow examination for confirmed diagnosis. It is a well-known fact that thrombocytosis may be a marker of inflammation, but low platelet count can be a significant alarming sign for severe infection and infection-induced immunosuppression [18]. Microbial endotoxin can cause endothelial damage, platelet adhesion and/or its removal from the bloodstream [19].

Thrombocytopenia may occur due to platelet destruction by the immune system. A positive Coombs test in most patients with brucella, response to corticosteroid, and detection of anti-platelet antibodies are the evidence of such mechanism [20].

In general, low platelet count may be due to the production failure in the bone marrow, being trapped in an enlarged spleen, or damaged in the peripheral circulation. Thrombocytopenia due to infectious diseases occurs because of bone marrow suppression, hypersplenism, hemophagocytosis, immunologic destruction of the cells, and DIC [21, 10].

Granuloma formation in the bone marrow is added to the etiologies of thrombocytopenia in brucellosis [22]. In one study [23], bone marrow biopsy revealed hypercellular marrow in 75% and granuloma formation in 41% of the samples. Seventy-five percent of the patients with both thrombocytopenia and hypercellular marrow had splenomegaly, as well. In hemophagocytosis phenomena, active histiocytes play an important role in erythrophagocytosis, leukophagocytosis, and platelet phagocytosis. Hemophagocytosis occurs not only during the course of brucellosis, but also in many infectious and noninfectious diseases including viral, fungal, bacterial, parasitic, malignant, and rheumatological diseases [24].

Despite the existence of thrombocytopenia, the bone marrow may be hypercellular with sufficient megakaryocytes or hypocellular [25, 23]. Therefore, bone marrow suppression is not a good explanation for thrombocytopenia. Hence, other etiologies should be considered for this cytopenia. One of the significant causes of thrombocytopenia is stimulated autoimmune phenomena induced by brucella bacteria that may lead to bleeding, purpura, and hemolytic anemia [26]. Moreover, monoclonal hypergammaglobulinemia and cryoglobulinemia are rare complications of brucellosis [27].

Hemorrhagic fevers in endemic areas, hematologic malignancies, as well as idiopathic thrombocytopenic purpura (ITP) should be considered as the differential diagnosis of brucellosis, even if the patient is afebrile at the time of admission [28]. Brucellosis and CCHF are both common in rural areas of endemic regions. They affect farmers and shepherds. Both of these diseases cause fever, rigors, thrombocytopenia, and bleeding, sometimes without other signs

and symptoms. However, the main difference is a significant reduction in incidence of Crimean-Congo in the winter due to inactivity of the carrier ticks [29] while brucellosis continues to occur. Severe thrombocytopenia and/or hemorrhage are characteristic clinical features of severe CCHF but they rarely occur in brucellosis. Finally, serologic tests, viral polymerase chain reaction, and obvious contact of CCHF patients with blood and tissues of sick animals or other affected patients, as well as history of tick bite will confirm the diagnosis of CCHF.

In case of brucella induced thrombocytopenia, severe thrombocytopenia and bleeding of the urinary tract, skin, gastrointestinal tract, as well as hemoptysis and hematemesis rarely occur [30]. As mentioned above, hematological changes are mild and subside with anti-brucella treatment, but even severe bleeding can be improved with antibiotic and hematologic supportive therapy [31]. In emergent cases with severe thrombocytopenia and bleeding, a short trial of intravenous immunoglobulin (IVIG) has been recommended to increase platelet count and to control bleeding. In the patients with platelets count of less than 10.000 mm^3 , corticosteroid therapy would be effective [4, 32]. However, in rare cases of severe and refractory thrombocytopenia, splenectomy may be helpful [33]. In one study [34], among 19 patients with severe thrombocytopenia, 10 received corticosteroids for less than two months and responded well to the treatment. Seven patients received corticosteroid for more than two months, 4 of them recovered and 3 underwent splenectomy and finally recovered. Two out of 19 patients died.

2. Summary

Brucella induced severe thrombocytopenia and pancytopenia imitates several hematological diseases. Not only infectious disease specialists, but also other experts in other fields such as gynecology, gastroenterology, hematology, ENT, dermatology, and urology should be familiar with brucellosis and its uncommon clinical pictures including bleeding and thrombocytopenia. All physicians should be aware of infectious diseases such as brucellosis and CCHF, which may be presented with severe thrombocytopenia and have to include them in the differential diagnosis of any disorder with thrombocytopenia and bleeding, even in afebrile patients. In these conditions, the patient's occupation and/or a minor fever may provide important clues to the diagnosis of infectious diseases such as brucellosis.

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