

Sarcoidosis and Cold Autoimmune Hemolytic Anemia: A Rare Association

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Receiving date: October 4, 2016; Accepted date: October 20, 2016; Published date: October 27, 2016

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Abstract

We present a 56 year old female patient with medical antecedents of sarcoidosis presenting a cold antibody autoimmune hemolytic anemia. A good response to corticosteroid treatment was achieved during hospitalization.

Keywords: Sarcoidosis; Autoimmune hemolytic anemia (AIHA); Red blood cells (RBC)

Introduction

Sarcoidosis is a multisystem granulomatous disorder of unknown etiology that affects individuals worldwide and is characterized pathologically by the presence of noncaseating granulomas in involved organs. The clinical presentation of sarcoidosis is variable but frequently involves the lungs and can have numerous extrapulmonary manifestations including skin, joint, cardiac, and eye lesions

Case Report

This is a 56 year old female patient with previous antecedents of multiorgan sarcoidosis since 1998. At that time she presented with diffuse adenopathies, parotiditis, uveitis and parenchymal pulmonary disease. A first pulmonary flair was described one year later and a second one two years after diagnosis. A third flair consisting of cutaneous involvement was described in 2002, the patient was on corticoid treatment which she voluntarily abandoned. No medical follow-up since then. She was complaining of generalized and progressive malaise over three weeks. Initially evaluated by her primary doctor, a routine blood test revealed hemoglobin of 6.6 g/dl with normal corpuscular volume. She was immediately referred to our hospital. Upon arrival the patient was pale but didn't look severely ill. The physical exam revealed normal blood pressure and heart rate but a slight hepatosplenomegaly was found. The initial laboratory tests revealed Hb 6.5 g/dl, MVC 84 fl and 222.7 giga/l (8.98%) reticulocytes, haptoglobin was inferior to 0.08 g/dl. Coombs test was positive with the presence of IgC3 antibodies. The chemical panel revealed normal renal function and electrolytes including protein C reactive and uric acid but liver function test revealed increase values of total bilirubin based on indirect one as well as slightly increase of aminotransferases. Viral serology for VIH, HBV, HCV, EBV, syphilis and CMV returned negative. Skin tuberculin test (PPD) was negative. Angiotensin converting enzyme was within the normal range and antinuclear antibodies were negative. A complete CT scan was ordered which confirmed the presence of homogenous hepatosplenomegaly as well as mediastinal adenopathies and interstitial pulmonary disease. Respiratory function tests revealed a restrictive syndrome already known

The echocardiogram showed normal left ventricular function, absence of ventricular hypertrophy but light mitral and tricuspid insufficiency as well as discrete pulmonary hypertension. A PET SCAN aiming at evaluating both the presence of active granulomas and the disease activity was ordered but only showed the previous described visceromegalies and adenopathies but no additional abnormalities.

The bone marrow examination revealed the presence of a reactive lymphocytosis and plasmacytosis. The patient was diagnosed of autoimmune hemolytic anemia (AIHA) as evidenced by the lab test and was initially put on IV steroids (1 mg/kg/d) without achieving a good biological response after 6 days of treatment so it was increased to 1.5 mg/kg/d. Four days later, good biological response was observed, hemoglobin and haptoglobin raised and reticulocytes and total and indirect bilirubin started to go down. Intravenous treatment was switch on to oral one and the patient was released at day 15 after admission.

Discussion

Sarcoidosis is a systemic disease of unknown origin, any organ can be affected and several immunological abnormalities have been reported.

This case shows a middle age female patient with previous antecedents of sarcoidosis presenting with moderate-severe autoimmune hemolytic anemia. This case reinforces the fact that sarcoidosis might play an important role in the development of other autoimmune diseases. In this regard, many autoimmune diseases have been related to sarcoidosis in the literature, especially Sjogren's syndrome, pernicious anemia and idiopathic thrombocytopenic purpura [1]. Rasha et al. described a patient presenting with pulmonary sarcoidosis and positive Coombs test with warm antibodies responding well to oral prednisolone [2]. Kondo et al. reported one patient with long standing sarcoidosis as in our case but presenting with AIHA, Sjogren's syndrome and idiopathic thrombocytopenic purpura [3]. There are few case reports of AIHA with sarcoidosis, one was also a middle age woman presenting with AIHA, warm antibodies and pulmonary sarcoidosis that responded well to steroid therapy [4] and the other case of AIHA was described in association with pure bone marrow sarcoidosis [5]. In all these cases, pulmonary sarcoidosis as associated to warm and not cold antibodies. AIHA due to warm antibodies has been reported in a patient with sarcoidosis localized in the right parotid gland [6].

Sarcoidosis is considered to result from an uncontrolled granulomatous immune response. T lymphocytes and specially T helper play a central role in this immune reaction [2,7]. Th-1 cells assist macrophage activation through secretion of interferon gamma as well as CD8 cytotoxic T cells through the secretion of interleukin [2]. Th2 cells assist antibody production by B cells through secretion of IL4, 10 and 13. Th1 cells are postulated to be under direct control of Th2 cells. This Triggering antigen in sarcoidosis or other autoimmune diseases leads to preferential induction of Th1 type CD4 cells and down regulation of Th2 type cells which could give rise to potential autoimmunity. All this process may lead to many autoimmunity diseases develop and could explain the link between sarcoidosis and hemolytic anemia [2,8]. Secondary inflammation due to autoimmune stimulation, cytokine and chemokine release could be possible mechanisms involved in autoimmunity and lymphomagenesis [9,10]. Besides, epigenetic mechanisms may play a major role in dysregulation of T-helper 17 (Th17) or T-regulatory (Tregs) cell homeostasis, Tregs and Th17 imbalance contributes to both autoimmunity and hematologic malignancies [11,12], that's why a bone marrow examination was performed to rule out the coexistence of Non Hodgkin lymphoma, sarcoidosis and hemolytic autoimmune anemia.

Was the AIHA arising in the setting of active sarcoidosis? The degree of disease activity was evaluated taking into consideration clinical, radiology, laboratory and functional respiratory test. In this regard, we were not able to identify worsening of previous disease localizations or presence of new ones, uveitis, cutaneous or articular involvement. The pulmonary disease involvement has not progressed compare to the previous CT available. Besides, the respiratory function tests did not worse in relation to that of the previous year. ACE level was within the normal range as well as calcium and B2 microglobulin. The PET SCAN exam was performed not only to rule out other coexistence conditions but to might have a regard over the response to treatment as hyper fixation is considered to be a marker of therapeutic response. In whole of this clinical picture, bronchoscopy was desestimated.

The treatment of cold AIHA should be confined to patients with symptomatic anemia and/or the presence of RBC transfusion dependences. RBC transfusion can be performed relatively safe compared to warm AIHA; the efficacy of corticosteroid treatment has not been confirmed, being effective in reduced fraction of patients up to 35% as in our case. Splenectomy is usually not effective since RBC destruction by C3b mediated opsonization primarily occurs in liver, not in spleen. However, rituximab has been recommended as the first

line treatment in patients with cold AIHA, providing response rates of 60% and duration of median 1 year [13,14,15].

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