

Case Report

Pulmonary Sarcoidosis and Autoimmune Hemolytic Anemia: Possible Common Immune Pathogenesis

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Abstract

A 49-year-old female presented with autoimmune hemolytic anemia and positive warm antibodies. She was diagnosed with chronic pulmonary sarcoidosis. The patient was given prednisolone after which she had complete remission of autoimmune hemolytic anemia and stabilization of her pulmonary status. A review will follow on association of sarcoidosis with autoimmune disease and its possible role in the development of such phenomenon.

Keywords: autoimmune hemolytic anemia, immunology of sarcoidosis, pulmonary sarcoidosis

Introduction

There has been an awareness of sarcoidosis for more than 100 years. It is a systemic disease of unknown origin characterized by non-caseating granulomas, affecting any organ in the body with either a self-limited or chronic course, or episodic with remissions and relapses. Multiple presentations of this disease are the basis of the theory that sarcoidosis has more than one cause, each probably contributing differently, thus allowing diverse clinical presentations.¹

Considerable research has been conducted exploring the immunology of sarcoidosis, particularly the T-cell lymphocyte population. The prevailing hypothesis is that sarcoidosis is a unique cell-mediated type of autoimmune process.² Such a theory can link sarcoidosis to other autoimmune phenomenon existing in the same patient. The following case report is an example of such an uncommon association.

Case Report

A 49-year-old Kuwaiti lady, referred to the medical outpatient at Amiri hospital in October, 1999 because of non-specific abdominal pain. She had no significant medical history. Physical examination was normal apart from mild pallor. Upon further evaluation her chest X-ray revealed bilateral diffuse fibrotic changes, more on the left side (Figure 1). Complete blood count reported normal WBC and platelets with a hemoglobin of 89 gm/L and high mean corpuscular volume. ESR was 120/hour. The patient was diagnosed with autoimmune hemolytic anemia (AIHA) as evidenced by blood smear, high reticulocyte count and positive Coombs test with warm antibodies (both direct and indirect). The following tests were within normal limits: arterial blood gas,

liver and renal functions, antinuclear factor, rheumatoid factor, complements, s-B12, RBC-folate, and G6PD. Serum immunoglobulin electrophoresis reported polyclonal gammopathy. Skin tuberculin test (PPD) was negative. S-angiotensin converting enzyme was high at 97ui/L (upper limit of normal: 90ui/L). The patient had a normal abdominal ultrasound; however, high resolution CT-scan of the chest reported large bilateral areas of consolidation in the mid-lung zones, which extended to the upper lobe in the left lung, as well as areas of interstitial fibrosis with reticular and honeycomb appearances in different zones. The results were in line with a diagnosis of pulmonary sarcoidosis (Figure 2).



Figure 1. CXR with diffuse reticulonodular changes.

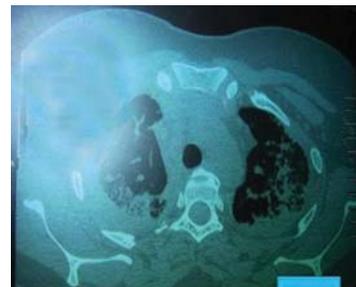


Figure 2. HRCT scan of the chest suggestive of pulmonary sarcoidosis.

Gallium scan reported increased uptake in both lungs and hilar regions suggestive of active sarcoidosis. Pulmonary function test reported a mixed pattern of lung disorder with predominantly restrictive element and grossly reduced

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Accepted for publication: 29 September 2010

transfer factor, confirmatory for sarcoidosis.

Bronchoscopy was performed; however, tissue was inadequate for transbronchial biopsy. Bronchoalveolar lavage for acid-fast bacilli was negative. Therefore, a thoracoscopic lung biopsy was done and histopathology reported focal granulomatous inflammation with interstitial pneumonia and interstitial fibrosis, highly suggestive of sarcoidosis (Figure 3).

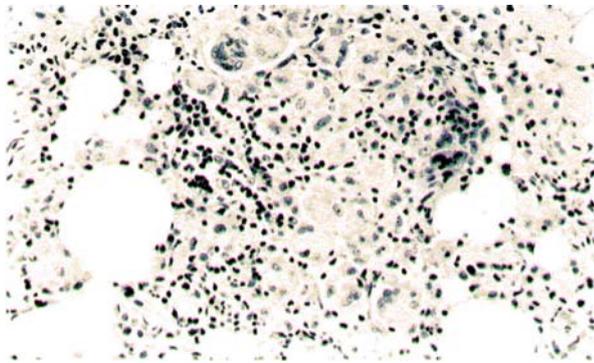


Figure 3. Histopathology of lung biopsy (Hematoxylin and eosin stain, 4X) showing non-caseating granuloma (arraw) diagnostic of sarcoidosis.

A diagnosis of pulmonary sarcoidosis presenting as AIHA was established and the patient took oral prednisolone (60 mg per day). Of note, she required a blood transfusion due to a further drop of her hemoglobin. Steroids were tapered after six weeks, by 10 mg every two weeks until a dose of 40 mg was reached. The patient maintained that dose for almost a year before it was tapered slowly. She has been off steroids for at least four years and clinically remains asymptomatic. Her last hemoglobin was 135 gm/dL with a normal reticulocyte count and negative Coombs test. Follow up pulmonary functions showed marginal improvement with 8% increase in flow and increased transfer factor. Chest X-ray showed some improvement (Figure 4).



Figure 4. CXR after steroid therapy.

Discussion

This case illustrates a middle aged lady with symptoms of hemolytic anemia severe enough to require blood transfusion. As she was further evaluated she had an associated picture of chronic pulmonary sarcoidosis, classified radiologically as grade III. Corticosteroids were initiated due to

the presence of stage III pulmonary disease with evidence of active granulomatous inflammation and autoimmune hemolytic anemia. She had good clinical response with remission of AIHA and marginal improvement followed by stabilization of pulmonary function. Corticosteroids have been tapered off quite slowly over almost 18 months and she has been in remission since that time.

This case reinforces the concept in the literature that sarcoidosis might play an important role in the development of autoimmune disease. Multiple autoimmune diseases have been reported in the literature in association with sarcoidosis, including a high frequency of endocrine autoimmunity, polyglandular autoimmune syndromes, idiopathic thrombocytopenic purpura, Sjogren's syndrome, gastrointestinal immune reactivity, pernicious anemia, and connective tissue disease.³ AIHA, however, has been uncommonly reported. The following review illustrates an etiological relation rather than observed association.

Sarcoidosis, a systemic disease of unknown etiology, is characterized by the presence of non-caseating granulomas, mainly in the lymph nodes, lungs, eyes, and skin. Any organ can be affected and several immunological abnormalities have been demonstrated. A number of etiological theories are implicated, which are primarily of environmental, infectious, genetic, and immunologic origins. Environmental factors such as socioeconomic class, access to health care, and the possibility of exposure to environmental agents have all been researched.¹ Current evidence points to genetic predisposition and exposure to unknown transmissible agent and/or environmental factors as etiologic agents.⁴ Cases where sarcoidosis have been transmitted by cardiac and bone marrow transplant suggest an infective agent¹ of which mycobacteria are the main suspected organisms. A recent study has demonstrated positive mycobacterium DNA-PCR in samples of patients with sarcoidosis.⁵

Genetic factors play an important role as explained by differing susceptibilities to immune regulation, T-cell function, or antigen presentation. Genetic factors can define the risk of disease and determine both disease pattern and prognosis. Multiple serologic studies showed primary associations with class I HLA-A1 and B 8, and class II HLA-DR 3 in Caucasians and similar findings have been reported in other autoimmune disorders.¹ A recent study found an interesting association between angiotensin converting enzyme (ACE) levels, ACE genotypes (DD, ID or II), and the presence of autoimmune manifestations in sarcoidosis. This study confirmed significantly higher ACE levels in sarcoidosis patients with autoimmune disease. The frequency of the ACE DD genotype significantly increased in patients with concurrent major granuloma masses (radiologically stage III pulmonary disease).⁶

Sarcoidosis was originally viewed as a defect of cellular immunity because of its association with cutaneous anergy. However, this misconception has been replaced by the interest-

ing theory that sarcoidosis is a unique cell-mediated type of autoimmune process. Sarcoidosis is thought to result from an uncontrolled granulomatous immune response. T lymphocytes are the essential component of this immune reaction. In sarcoidosis, a T helper 1(Th1) response is an essential event and an up-regulation of interleukin-12 (IL-12) has been observed in diseased sites.⁷ An unidentified initiating factor triggers lymphocyte activation and proliferation in the first place. The recognition of such antigens is through specific receptors expressed on the cell membrane of T cells. Several studies have demonstrated the presence of oligoclonal T-cell populations in the blood and lungs of sarcoidosis patients, which supports the conclusion that antigen-induced immune response plays a role in sarcoidosis pathogenesis.^{2,8}

T-helper lymphocytes (CD4) when triggered start lymphokine production, recruitment of monocytes and contribute to the mechanism of hyperglobulinemia through their effect on B cells. An interesting theory that CD4 cells, contain different subsets, of interest are the Th-1 and Th-2 types, which can be involved in the pathology of the problem.

Th-1 cells assist macrophage activation through secretion of interferon-gamma as well as CD8 cytotoxic T cells through the secretion of interleukin-2 (IL-2). Th-2 cells assist antibody production by B cells through secretion of IL-4, 10, and 13. Th-1 cells are postulated to be under direct control of Th-2 cells. The triggering antigen in sarcoidosis or other autoimmune diseases leads to preferential induction of Th-1 type CD4 cells and down regulation of Th-2 type cells which, in theory, gives rise to potential autoimmunity. In other words, when control of these autoreactive T-cells breaks down, autoimmunity in the form of different diseases develops. Such a theory can help explain the co-existence of similar types of autoimmune responses to different antigens within the same individual and family groups and why new autoimmune phenomena can arise in a patient with a pre-existing autoimmunity.⁹

Identification and modulation of mediators of such a reaction represent a promising approach for the development of more specific therapeutic agents.

A literature review revealed that sarcoidosis associated with autoimmune diseases was reported by several authors. One patient with long standing sarcoidosis developed AIHA, Sjogren's syndrome and idiopathic thrombocytopenic purpura.¹⁰ Another interesting case report of sarcoidosis in a patient who developed polyglandular autoimmune syndrome type III, Grave's disease, insulin-dependent diabetes mellitus and celiac disease. One patient with vertigo, Grave's disease and pernicious anemia concurrently with sarcoidosis was described in addition to another patient with thyroiditis, Addison's disease, Sjogren's syndrome, and sarcoidosis.³

Three cases with connective tissue diseases that developed pulmonary sarcoidosis have been reported.¹¹ A rare case report was published of a 35-year-old man with venous thrombosis, diagnosed as antiphospholipid syndrome, who later

developed pulmonary sarcoidosis.¹²

There were few case reports of AIHA with sarcoidosis. One was of a middle aged woman who presented with AIHA, warm antibodies and pulmonary sarcoidosis that responded well to steroid therapy.¹³

Another case of AIHA was described in association with pure bone marrow sarcoidosis.¹⁴ AIHA due to warm antibodies has been described in a female patient with sarcoidosis localized in the right parotid gland.¹⁵

Such clinical cases reported support the concept of an underlying common genetic and immunopathogenic theory linking sarcoidosis to other autoimmune phenomena rather than just an accidental correlation.

Sarcoidosis is an interesting disease to research for its pathology as well as new treatment strategies. At present there is enough evidence to support the concept of sarcoidosis as an autoimmune process. Isolation of the granulogenic factor is an exciting finding that can open the door for new therapies.

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