Familial sarcoidosis: Report of a mother and her son
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Abstract

Sarcoidosis is a chronic, multisystemic inflammatory disease, characterized with noncaseating granulomas. The pathogenesis of the disease is not yet clear, however, the main hypothesis is impaired and inadequate immune response developing against different environmental triggers in genetically predisposed people. The role of genetic factors in the development of sarcoidosis is well known. Over many years, familial sarcoidosis cases have been reported in various studies. In this report, we present familial sarcoidosis cases in a mother and her son.

Keywords: Sarcoidosis, familial, presentation

Introduction

Sarcoidosis is a multisystemic inflammatory disorder of unknown etiology, which is characterized by T-lymphocyte infiltration, granuloma formation, and impairment of the normal microarchitecture (1). Bilateral hilar lymphadenopathy, pulmonary infiltration, and skin, eye and locomotor findings are important clinical findings. Sarcoidosis develops in genetically predisposed patients as a result of the cellular immune response triggered by one or more antigens (2). All races and ethnic groups can be affected. Some studies have shown that the class 2 MHC allele are associated with susceptibility to disease development and/or with disease phenotype. The relationship between non-Human Leukocyte Antigen (HLA) genes and sarcoidosis has been investigated but the results are still incompatible (3). The existence of familial predisposition is known for many years and familial sarcoidosis cases have been reported (4). In this case, we presented familial sarcoidosis cases observed in a mother and her son.

Case Presentations

Case 1
A 50-year-old female patient with complaints of bilateral ankle joints arthritis, morning stiffness, fatigue, and effort dyspnea was admitted to our rheumatology clinic. Patient medical history indicated that she had hypertension lasting 2 years under control with antihypertensive drugs. On physical examination, bilateral ankle joint arthritis with reduced range of motion was detected. Laboratory tests, including hemogram, fasting blood sugar, urinalysis, and liver and renal function tests were normal. Acute phase reactants were examined: erythrocyte sedimentation rate (ESR): 45 mm/h (normal, <25 mm/h), C-reactive protein (CRP): 4.12 mg/dL (normal, <0.5 mg/dL). Thyroid function tests, serum tumor markers, and serum amyloid A were normal. Serum angiotensin-converting enzyme (ACE) level was 156 mg/dL (normal, <45 mg/dL); serum calcium and 25-hydroxy vitamin D3 were normal. Serologic tests were performed; complement, rheumatoid factor (RF), antinuclear antibody (ANA), antineutrophil cytoplasmic antibody (ANCA), and anticyclic cytrullinatedpeptidantibody (anti-CCP) were negative. On abdominal ultrasonography hepatosteatosis and myoma at the uterus was reported. Chest X-ray showed enlarged hilar lymphadenopathies (Figure 1). On thoracic computed tomography (CT), bilateral hilar and mediastinal lymphadenopathies (largest, 38×20mm) and multiple nodules spreading over whole areas but more significantly at the upper and middle zones of both lungs were reported (sarcoidosis grade 2; Figure 2). A chest disease specialist was consulted and endobronchial ultrasonography (EBUS) was performed. On histopathological evaluation noncaseating granuloma formation compatible with sarcoidosis was reported. In terms of extrapulmonary involvement (skin, eyes, neurosarcoidosis), the patient was investigated but no findings were detected. Differential diagnosis was conducted; lymphoma, fungal infection, and tuberculosis were excluded. The treatment was started with corticosteroids 32mg/day and hydroxychloroquine 200 mg/day. Six month later, clinical laboratory and radiologic regression was observed. The patient with fine general condition is in the clinical follow-up program.

Case 2
A 27-year-old male patient with complaints of bilateral knee and ankle joints pain, morning stiffness, and fatigue was admitted to our rheumatology clinic. Patient medical history indicated that his mother has had...
sarcoidosis. Physical examination findings were normal. Laboratory tests were performed; hemogram, urinalysis, fasting blood sugar, and liver and renal function tests were normal. Acute phase reactants were examined, including ESR, 2 mm/h (normal, <25 mm/h) and CRP, 0.06 mg/dL (normal <0.5 mg/dL). Thyroid function tests, serum tumor markers, and serum amyloid A were normal. The serum ACE level was 92 mg/dL (normal, <45 mg/dL); serum calcium and 25-OH Vitamin D3 were normal. Serologic tests were performed; complement, RF, ANA, ANCA, anti-CCP antibodies were negative. On the thoracic CT, multiple mediastinal and bilateral lymphadenopathies were detected. A chest disease specialist was consulted and EBUS was performed. Noncaseating granuloma was reported on pathological examination (Figure 3).

The patient was diagnosed with sarcoidosis and a nonsteroidal anti-inflammatory drug (NSAID) was started. Six months later, the patient’s locomotor system complaints was regressed and no pathologic findings in control thorax CT imaging was observed. The patient with fine general condition is still in the clinical follow-up program without any treatment. Informed consent was obtained from both patients.

Discussion
We report herein the familial sarcoidosis cases in a mother and her son. While the mother...
has had a more aggressive disease and was treated with corticosteroids, her son has had less complaints and the disease was regressed without any treatment. Both patients were investigated for extrapulmonary involvement but no findings were detected. Familial cases of sarcoidosis have been reported for years. Different trials have reported rates of familial sarcoidosis between 1% and 19% (5). In earlier twin studies, the rate of sarcoidosis was reported to be higher in monozygotic twins compared to dizygotic twins. A Case-Control Etiological Study of Sarcoidosis (ACCESS) trial revealed that the relatives of patients with sarcoidosis had a 5-fold higher risk of sarcoidosis compared to the control group (6). In another study, while the risk of sarcoidosis was increased 80-fold among monozygotic twins in the Danish and Finish populations, this rate was detected to be increased only 7-fold in dizygotic twins (7). These observations suggested that certain genetic variations could affect the development and the clinical presentations of sarcoidosis. In various studies, the correlation between Class 2 MHC alleles and the predisposition to the disease or phenotype was detected (Table 1). For example, a strong relationship was detected between HLA-DQB1*0201 and HLA-DRB1*0301 alleles and acute onset disease, erythema nodosum, and a good prognosis of diseases. Also, a correlation between chronic and severe sarcoidosis and HLA-DQB1*1501 and HLA-DQB1*0602 alleles were reported. While HLA-DRB1*01 and HLA-DRB1*04 were negatively correlated with sarcoidosis, HLA-DRB1*03, HLA-DRB1*11, HLA-DRB1*12, HLA-DRB1*14, and HLA-DRB1*15 genes were reported to represent an increased risk for sarcoidosis (8). In studies investigating the association between non-HLA genes and sarcoidosis (Table 2), TNF-308A allele gene polymorphism was detected to be correlated with Lofgren syndrome (9). In patients with sarcoidosis, a correlation was detected between butyrophilin-like 2 gene (BTNL2) and sarcoidosis, independent of the HLA-DRB1 variation (10). Hofmann et al. (11) investigated 499 German patients with sarcoidosis and detected an association between the Annexin A11 gene and sarcoidosis. Annexin A11 has the functions of apoptosis, calcium-mediated signaling, and regulation of the cell traffic. Dysfunction of the Annexin A11 gene may affect the apoptosis pathways and mechanisms in sarcoidosis. In the literature, there are reports about the familial sarcoidosis cases. Salm (12) reported a familial sarcoidosis patient who terminated as a candidate of sarcoidosis. Brennan et al. (13) reported the high prevalence of sarcoidosis among siblings (2.4%), which suggests that genetic familial factors significantly predispose the development of sarcoidosis and that family members of affected patients should be screened for this disease. Pietinalho et al. (14) compared the prevalence of sarcoidosis among Finnish and Japanese populations. Those surveys provide the prevalence of familial sarcoidosis in Finland of 3.6%-4.7% and in Hokkaido of 2.9%-4.3%. Among familial cases, the dominating relationships were sister-brother and mother-child relationships. Elford et al. (15) reported a family in which five members have been affected with sarcoidosis. The radiological findings of all cases are presented, together with HLA typing, T-cell subset, and cytokine analysis in four cases.

In conclusion, the association of many HLA/non-HLA genes and sarcoidosis has been investigated in the recent years (16-29); however, the results are controversial and inconsistent. The familial sarcoidosis cases are reported in various studies. Sarcoidosis is more common between the relatives of patients with sarcoidosis than the normal population. The relatives of patients with sarcoidosis should be investigated as a candidate of sarcoidosis.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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