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Prognostic Factors in Sarcoidosis

Cuneyt Tetikkurt*

Pulmonary Diseases Department, Istanbul University, Turkey

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***Corresponding author:** Cuneyt Tetikkurt, Pulmonary Diseases Department, Cerrahpasa Medical Faculty, Istanbul University, Turkey, Email: tetikkurt@gmail.com

Introduction

Sarcoidosis is a chronic disease of unknown origin that is characterized by the formation of noncaseating granulomas in the affected organs, predominantly in the lungs and the intra thoracic lymph nodes. Inflammation is mediated by lymphocytes of Th1 phenotype that lead to formation of non-caseating granulomas. The granulomas are the pathologic hallmark of the disease that usually occur in the bronchial sub mucosa [1,2]. Prognosis is excellent with a spontaneous resolution in 85% of the stage I patients. Advanced pulmonary disease develops in approximately 5% of the sarcoidosis patients causing death in less than one percent by lung fibrosis [3,4]. Chronic pulmonary disease usually develops over one or two decades. Prognostic factors for persistent pulmonary disease become evident within two years following diagnosis [5,6].

Currently, there are no specific benchmarks to predict the development of persistent pulmonary sarcoidosis. Although sarcoidosis may show a progressive course with relapse and remissions, it does not always lead to end stage pulmonary fibrosis [7]. The mechanisms for the variable course and outcome of sarcoidosis are unknown. The granuloma burden in sarcoidosis appears to be the hallmark of persistent and progressive disease. The kinetics of granuloma formation is variable between individual patients [8] as well as the dynamics of different organ involvement in the same patient. Treatment of sarcoidosis depends on the supression of granuloma formation and stabilization of organ function. Although numerous risk factors like lupus pernio, cystic bone lesions, hypercalcemia, and multiple organ involvement have been defined for advanced pulmonary sarcoidosis, no study has precisely established the clinical markers for persistent disease. This may be associated with the fact that outcome of sarcoidosis is dependent on many factors including genetic, hormonal, and environmental effects.

Identification of patients with a potential risk factor for advanced disease is the most crucial point in the follow-up of sarcoidosis patients. In this review, the aim is to discuss the potential prognostic factors that play a role in lung fibrosis and in other unfavorable outcomes of sarcoidosis. Since the disease shows a variable course with relapses and remissions, the most critical endpoint for clinicians is to diagnose patients that may show a chronic course resulting with end-stage pulmonary fibrosis and commit early treatment to suppress granuloma formation leading to organ dysfunction.

Clinical Prognostic Factors

Monitoring disease severity is the fundamental point for clinical management of sarcoidosis patients. Previously, pulmonary function trends and chest radiology have been the benchmark for patient follow-up and prognostic evaluation. Serial pulmonary function and radiologic evaluation are not sensitive markers to identify patients with a severe prognosis. The heterogeneity of pulmonary function tests in sarcoidosis is well known. Lung function impairment is usually greater in severe parenchymal disease, especially in patients with stage III and IV while the same pulmonary function pattern may be observed in earlier stages of the disease. A restrictive pattern is observed in approximately 30-50% of the patients and a significant obstructive functional impairment may also be present [7,9-11].

Initial lung function may be useful for prognostic evaluation of sarcoidosis. Viscum has reported that patients with a FEV1 less than 50% of predicted had an increased mortality risk of 4.2 compared to patients with normal function. Bronchial obstruction was also associated with an increased mortality risk [12]. Mana et al. [6] have shown that low initial FVC may a predictor of chronic sarcoidosis [13]. In contrast to unfavorable prognostic value of initial lung function, Judson has shown that majority of the patients had stable FVC and FEV1 after two years [3]. A decreased DLCO may occur in sarcoidosis patients compatible with other intertitial lung diseases [14]. Impairment of gas transfer usually occurs in advanced pulmonary sarcoidosis there by is not a reliable prognostic parameter. The six-minute walk test (6MWT) may reveal decreased exercise capacity in sarcoidosis. Desaturation depends on many factors including

lung function, cardiac status, and muscle strength. Reduced (6MWT) is usually associated with advanced lung disease in sarcoidosis.

Lung function tests are insensitive as prognostic markers for sarcoidosis patients. First, no single pulmonary function variable is indicator of disease severity. Second, pulmonary functions are dependent on many factors including cardiac status, muscle strength, patient performance, and co morbid diseases. Third, there are no current thresholds for significant changes to indicate a severe or chronic outcome for sarcoidosis. Fourth, the low accuracy of pulmonary function tests due to over or underestimation of the results render them as insensitive prognostic markers. As a result, pulmonary function trends do not always represent disease severity and thereby indicate a chronic outcome.

Chest radiology has been the most frequent routine clinical tool for the evaluation of sarcoidosis patients. Scadding was the first radiologist to reveal the effect of radiologic stage for prognosis and stated that in stages I and II the remission was significantly high compared to stages III and IV [15]. Reich and Viskum confirmed the association between persistent chronic sarcoidosis and advanced radiologic stages III and IV. In their studies radiologic clearance was found to be a good prognostic sign while stage III was associated higher mortality [12,16]. Chest CT is superior to chest radiology in regard to its high spatial resolution to assess the lung parenchyma. HRCT is more accurate for diagnosis by detecting parenchymal distortion, presence and localization of micro nodules and early fibrotic changes. The HRCT findings of ground-glass opacity, nodules, septal thickening, and lineer opacities may be reversible while only architectural distorsion is irreversible [17-20]. Consequently, in the early stages (I and II) of sarcoidosis patients the diagnostic sensitivity and specifity of HRCT is not significant because these lesions do not have a predictive value. Later stages of sarcoidosis (III and IV) is frequently irreversible. When radiologically appearent, these lesions usually indicate irreversible and chronic disease. Therefore, the prognostic significance of this type lesion is not useful for predicting the patient prognosis in advance while in patients with radiologic stages I and II probability of remission sarcoidosis is high.

A number of laboratory markers including ACE, CRP, Ca, and neopterin have been used to asses active disease and prognosis. ACE is produced by macrophages within granulomas and reflects granuloma burden. Serum ACE is elevated in approximately in 60% of the patients but both the sensitivity and specifity is low. ACE is a marker of disease activity rather than prognosis. Serum calcium is elevated in about 11% while hypercalcuria is observed in 40%, and nephrocalcinosisin 10% of the sarcoidosis patients [21]. Persistent hypercalcemia or hypercalcuria may indicate a chronic disease [1]. Serum CRP may be useful to identify sarcoidosis patients with extensive and severe disease but the specifity is low [22]. Other inflammatory markers with indeterminate significance for prognosis are neopterin, IL-2, tryptase, IL-18, and KL-6. KL-6 is considered as the best prognostic indicator among these immunological markers.

Extra pulmonary organ involvement frequency in sarcoidosis is variable ranging from limited to ninety percent [1,3,21]. Multiorgan disease, defined as three or more organs is usually associated with a severe prognosis. Lupus pernio, chronic uveitis, cystic bone lesions, and nephrocalcinosis may be indicators of persistent disease [9,23]. On the other hand, cardiac and neurosarcoidosis cause a high mortality. Clinical diagnosis and involvement of these organs is discordant. Presence of spinal cord disease and intracranial mass are unequivocally relevant with a poor outcome. Recently Yanardag et al. [24] have shown that diffuse endobronchial involvement identified by bronchoscopic biopsy is a severe prognostic hallmark.

The role of genetics is well established in sarcoidosis patients. The frequency of sarcoidosis in the first degree relatives is significantly high and approaches to fifteen percent. HLA-DRB1 and HLA-DQB1 allels regulate the susceptibility to sarcoidosis [25,26]. The interaction between antigen, HLA II molecules, and T cell receptors is crucial for sarcoidosis. The DRB*301 is associated with occurrence of Löfgren syndrome with a benign prognosis while DR15 and DR16 genotypes have a persistent chronic disease [27,28].

HLA phenotypes may be relevant with specific organ involvement. HLA-DRB3 is associated with bone marrow disease, HLA-DPB1*0101 with hypercalcemia, and HLA-DRB1*0401 with salivary gland and eye involvement. HLA-B*07 and *08 are relevant with sarcoidosis risk [1-3,25]. HLA-DRB1*15 is more frequent in skin disease while HLA-DRB1*0803 in neurosarcoidosis [29].Genetic predisposition is the most important factor for the development of any disease. The interaction of genetic, hormonal, and environmental effects should be kept in mind for sarcoidosis. The variable course of sarcoidosis may also be explained by the different genetic phenotypes of the patients.

Conclusion

The presentation, clinical manifestations, and outcome of sarcoidosis is highly variable. Identification of sarcoidosis patients with a worse prognosis is the hallmark of a successful treatment. The heterogeinity of pulmonary function impairment and radiologic changes together with the limitations of significant change thresholds is the main dilemma for clinicians. Laboratory and genetic investigations share the same predicament to determine the outcome of sarcoidosis. Presence of various clinical factors like lupus pernio, cardiac, cerebral, or diffuse endobronchial involvement appear to be the best criteria to determine the prognosis. Cardiac or neurosarcoidosis are not helpful criteria since they are already manifestations of advanced disease in most of the patients. For precise identification of prognostic factors further studies with large and heterogenous

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sample sizes are needed. On the other hand, the sensitivity and specify of current prognostic factors like hypercalcemia, lupus pernio, multiple organ disease, and diffuse endobronchial involvement may be increased by performing further meta-analytic studies.

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