ORIGINAL ARTICLE

Pulmonary and extra-pulmonary manifestations of sarcoidosis

Sasan Tavana[1], Masoumeh Alizadeh[1], Seyed Amir Mohajerani[2], Seyed Mohammadreza Hashemian[2]

[1]Department of Pulmonary Medicine, Clinical Research and Development Center, Shahid Modarres Hospital, [2]Chronic Respiratory Diseases Research Center, National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran

ABSTRACT

Background: Sarcoidosis is a systemic multi-organ granulomatous disease of unknown etiology that is characterized by the presence of granuloma in various organs. The clinical features of sarcoidosis are heterogeneous but pulmonary involvement is cardinal manifestations. The aim of this study was to determine radiologic, clinical and laboratory findings of patients with sarcoidosis. **Patients and Methods:** In a cross-sectional study, all patients visiting sarcoidosis clinic were enrolled in the study. Computed tomography (CT) scan was obtained and lab exams were obtained from patient and reports were recorded in data sheet. **Results:** Total of 55 patients with sarcoidosis were enrolled in the study. The average of age was 44.6 (range 25-62) years. Thirty-seven patients were male and 18 were female. The most common extra-pulmonary manifestation was arthritis (in 18% of cases) and then lupus pernio (12.8%) and uveitis (10.9%). Bilateral hilar adenopathy and para tracheal lymphadenopathy was observed in 39(70%) and 22 (40%) of patients. Parenchymal nodules (30%), bronchiectasia (25%), ground-glass opacification (18%) were the most common findings. Percentages of patients with dyspnea were 29% and percentages of patients with cough were 21%. Among abnormal lab tests, high urine calcium (Ca) were positive in 21% and high angiotensin-converting enzyme (ACE) in 16% of patients. **Conclusion:** Pulmonary involvements are both fibrosis and granulomatosis and the most common manifestations are parenchymal nodules, bronchiectasia and high-grade fibrosis. The most common extra-pulmonary involvement is arthritis. Lab tests are non-specific and have no correlation with duration or severity of disease.

Key words: Sarcoidosis, pulmonary, extra-pulmonary

Address for correspondence:
Dr. Seyed Mohammadreza Hashemian,
Chronic Respiratory Diseases Research Center, National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran.
E-mail: iran.criticalcare@yahoo.com, smrhashemian@sbmu.ac.ir

INTRODUCTION

Sarcoidosis is a systemic multi-organ granulomatous disease of unknown etiology that is characterized by the presence of non-caseating granulomas in affected organs. Sarcoidosis affects males and females of all ages and typically young adults and is often present initially with bilateral hilar lymphadenopathy, pulmonary reticular pattern and involvement of the skin, joints or eyes. There is a positive relationship between the extent of granuloma infiltration and the levels of the different inflammatory mediators.[1]A cardinal feature of sarcoidosis is the presence of CD4+ T cells that interact with antigen presenting cells (APC) to initiate the formation and maintenance of granulomas.[2]

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The clinical features of sarcoidosis are heterogeneous and, although the lung is involved in over 90% of patients, multisystem involvement is characteristic of the disease.[3] Pulmonary disease is the most common manifestation requiring treatment. Clinicians must rely on guidelines and personal experience to manage their patients.[4]

Imaging has a prominent role in assessment of sarcoidosis diagnosis and outcome, which are extremely variable.[5] Chest radiography staging helps predict the probability of spontaneous remission, and stage IV is associated with higher mortality.[6] However, the reproducibility of reading is poor and inconsistent. Many patients are asymptomatic and diagnosed asa result of incidental chest radiograph or computed tomography (CT) scans. Therefore, clinicians need to recognize both pulmonary and extra-pulmonary radiologic manifestations of the

disease, take note of features that may be suggestive of sarcoidosis, in order to reduce associated morbidity and mortality.

This study determined the radiologic, clinical and laboratory findings of patients with sarcoidosis and their correlation to outcome.

PATIENTS AND METHODS

In a cross-sectional study, all patients visiting sarcoidosis clinic during 2012 and 2013 were enrolled in this study.

Patients with confirmed diagnosis of sarcoidosis in histopathology and age between 20 to 75 years were enrolled in the study. Exclusion criteria were patients with other pulmonary disease such as tuberculosis, patients with other systemic disorders.

All demographic data were collected including age, weight and sex. Then a CT scan was obtained and report was read by one radiologist. Lab exams were obtained from patient and sent to lab to measure angiotencin converting enzyme (ACE), serum and urine calcium (Ca), blood urea nitrogen (BUN), creatinine Cr), parathyroid hormone (PTH),phosphorous (p);1,25, OH- D3(vitamin D3), thyroid stimulating hormone (TSH). Stage of disease was determined by one single pulmonologist.

RESULTS

Total of 55 patients with sarcoidosis were enrolled in the study. The average of age was 44.6 (range 25-62) years. Thirty-seven patients were male and 18 were female. We investigate both pulmonary and extra-pulmonary involvements in these patients.

The most common extra-pulmonary manifestation was arthritis (in 18% of cases) and then lupus pernio (12.8%) and uveitis (10.9%). Extra-mediastinal lymph node involvement (10.9%) and granulomatosis mass (18%) were also frequently seen in our study. List of various extra-pulmonary manifestations are listed in Table 1.

Pulmonary involvements were also seen in all patients of our study (100%). Bilateral hilar adenopathy and paratracheal lymphadenopathy was observed in 39 (70%) and 22 (40%) of patients. Various pulmonary involvements are listed in Table 2. Parenchymal nodules (30%), bronchiectasia (25%), ground-glass opacification (18%) were the most common findings in our study. Obstructive pattern in pulmonary function tests (PFT) and restrictive pattern was observed in 32.5% and 67.5% of patients.

Patients were categorized based on their stage of sarcoidosis [Table 3]. Sixty-nine percent of patients were in stage 1 of and 10% were in stage 2 of the disease.

Interestingly, when patients with arthritis, uveitis, erythem nodosum (EN) were classified based on their stage of the disease. Higher percentage of patient in stage 1 had arthritis than uveitis and EN, while in stage 4 more patients had EN [Figure1].

Various pulmonary symptoms are listed in Table 4. Percentages of patients with dyspnea were 29% and percentage of patients with cough were 21% and patients with chest pain were 18%. Airway involvement was also

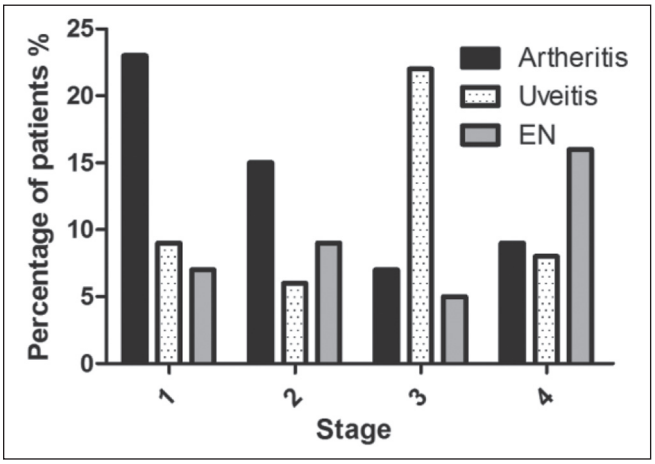

Figure 1: Percentage of patients with arthritis, uveitis, and Erythema Nodosum (EN) classified based on their stage.

Table 1: Extra-pulmonary manifestations of sarcoidosis

	Patients number (%)
Arthritis	10 (18.1)
Lupus pernio	7 (12.8)
Anterior uveitis	6 (10.9)
Eruthem nodusom	5 (9.1)
Enlarged lacrimal gland	3 (5.4)
Endobronchial cobblestoning	3 (5.4)
Cranial nerve involvement	5 (9.1)
Spinal cord involvement	3 (5.4)
Extra-mediastinal lymph-node involvement	6 (10.9)
Aspergilloma	6 (10.9)
Granulomatosis mass	10 (18.1)

Table 2: Pulmonary manifestations of sarcoidosis

	Patients number (%)
Bilateral hilar lymphadenopathy	39 (70)
Para tracheal lymphadenopathy	22 (40)
Parenchymal nodules	17 (30.9)
Bronchiectasis	14 (25.4)
Interstitial fibrosis	10 (18.1)
Perilymphatic nodules	4 (7.2)
Bronchiolitis	2 (3.6)

determined in our patients and cobble stoning (18%) and mucosal erythema (16%) were the most common findings.

Radiologic manifestations of pulmonary sarcoidosis in CT scan were classified based on two categories of granulomatosis inflammations and irreversible fibrosis. The most common finding in granulomatosis was nodules (both micro and macro) in 21% of patients. The most common irreversible fibrosis was traction bronchiectasis in 18% of patients. All various radiologic findings are depicted in Table 5.

Various abnormal lab diagnosis are depicted in Table 6. Sarcoidal granulomas produce ACE, and ACE levels are elevated in 16% of patients with sarcoidosis. Other abnormal lab tests were high BUN in 10% and high PTH in 12.7% of patients. High urine calcium (Ca) was observed in 22% and high serum Ca were observed in 9.1% of patients [Table 6].

In patients with high level of ACE, ACE did not have any correlation with duration of disease (r = 0.14, *P* = 0.78). Duration of disease also had no significant correlation with BUN (r = 0.18, *P* = 0.54), PTH (r = 0.22, *P* = 0.33) and urine Ca (r = 0.29, *P* = 0.20), serum Ca (r = 0.37, *P* = 0.082). In addition, duration of disease had no significant correlation with age of patients(r = 0.11, *P* = 0.45).

DISCUSSION

Sarcoidosis is a multi-organ disease with both pulmonary and extra-pulmonary involvements. Here in a cross-sectional study, we had surveyed 55 patients with sarcoidosis attending our clinic. All patients with sarcoidosis were evaluated for incidence of various manifestations and organ involvement of sarcidosis and lab exams and their relationship with stage of disease. Besides, radiologic manifestations of sarcoidosis were determined in these patients.

Among pulmonary manifestation, parenchymal nodules and bronchiectasia were the most common forms in our patients. Bilateral hilar and paratracheal lymphadenopathy have been observed in 70% and 40% of patients.[7] One of the most confusing features of sarcoidosis is its various pulmonary manifestations that could mimic many diseases in lung. As a matter of fact, sarcoidosis does not have specific manifestations in lung and therefore patients with only pulmonary manifestations are difficult to diagnosis per se.[8] On the other hand, sarcoidosis could imposture different pulmonary presentations. Sarcoidosisis characterized by a wide spectrum of radiological appearances. Imaging substantially contributes to the diagnosis of sarcoidosis.[9] Therefore, it is very important to determine the incidence of various radiologic manifestations in sarcoidosis. This would help to have a list of differential diagnosis and to rule out other diagnosis in patients with ambiguous manifestations and undetermined diagnosis.

Table 3: Patients classified based on their stage of sarcoidosis

Stage	Patients number (%)
1	38 (69)
2	6 (10.9)
3	8 (14.5)
4	3 (5.5)

Table 4: Pulmonary symptoms and airway involvements of sarcoidosis

Pulmonary symptoms	Patients number (%)
Dyspnea on exertion	16 (29.1)
Cough	12 (21.8)
Chest pain	10 (18.1)
Palpitations	9 (16.3)
Asymptomatic	8 (14.5)
Airway involvement	
Mucosal erythema	9 (16.3)
Mucosal oedema	6 (10.9)
Cobble stoning	10 (18.1)
Mucosal plaques	5 (9)
Mucosal granularity and nodules	4 (7.2)

Table 5: Radiologic manifestations of pulmonary sarcoidosis in computed tomography (CT) scan

Granulomatous inflammation	Patients number (%)
Nodules (Micro, Macro)	12 (21.8)
Consolidation	6 (10.9)
Ground-glass opacities	4 (7.2)
Irreversible fibrosis	
Traction bronchiectasis	10 (18.1)
Honeycomb-like opacities	8 (14.5)
Bullae	7 (12.7)
Ground-glass opacities	5 (9.1)
Interlobular septal thickening	3 (5.4)

Table 6: Number and percentage of sarcoidosis patients with abnormal laboratory findings

	Patients number (%)
High ACE level	9 (16.3)
High BUN	6 (10.9)
High PTH	7 (12.7)
High Urine Ca	12 (21.9)
High serum Ca	5 (9.1)
High serum P	1 (1.8)
High 1,25-OH-D3	1 (1.8)
High Alkalin phosphatase	0
High TSH	0
Positive proteinuria	0

ACE – Angiotensin converting enzyme; BUN – Blood urea nitrogen; PTH – Parathyroid hormone; Ca – Calcium; P – Phosphorous; D3 – Vitamin D3; TSH – Thyroid stimulating hormone

One important notion is that we did not found any association between pulmonary findings and severity of disease. Other researchers showed that the extent of pulmonary fibrosis is associated with the duration of disease.[10] But we did not find any correlation between stage of disease and duration of disease. Apparently, the severity and stage of disease is related to the degree of activity of immune system not the duration of activity, therefore, contribution of genetic and environmental factors induces immune system activation.[11] Giant cell granulomatosis is formed by immune cell activation in various organs composed of histiocytes, plasma cells, lymphocytes and fibroblasts. In addition, imaging patterns are indicative of reversible and irreversible disease; a nodular pattern is almost invariably reversible, reticular abnormalities and anatomic distortion denote irreversible fibrotic pattern, ground-glass opacification is variably reversible and may be indicative of alveolitis or fine fibrosis.[12]

Among extra-pulmonary manifestations, arthritis was the most common finding (18%) of patients. In total, about 39% of patients had extra-pulmonary involvement. Other reports depicted that arthritis is the most common extra-pulmonary symptom.

Among abnormal lab tests, high urine calcium (Ca) was positive in 21% and high ACE in 16% of the patients. However, the value of serum ACE levels in diagnosing or managing sarcoidosis remains controversial. Although ACE levels may be used,[13] as a diagnostic tool, measurement of serum ACE levels lacks sensitivity and specificity. For example, the positive and negative predictive values were only 84% and 74%, respectively.[14] Another important issue of our study was that none of lab tests had any correlation to the duration or severity of disease which indicates that lab tests are useful in diagnosis of sarcoidosis but with low sensitivity and specificity. Therefore, they should not be relied on unless other radiologic and pathologic findings are highly suggestive.

The propensity of sarcoidosis to induce diffuse fibrosis in later stage of disease was found in our study. Adenopathy was observed in all four stages at the same rate, but parenchymal nodules were the main manifestation in our patients. Diffuse fibrosis in stage 4 was the most common findings. Interestingly, extra-pulmonary involvements such as arthritis were more common in stage 1; and on the other hand, uveitis and EN were more common in stage 3 and 4. Although the association of stage of disease and extra-pulmonary involvement could not be concluded; however, the incidence of extra-pulmonary manifestations such as arthritis or EN in different stages could be inferred.

Our results showed that 10% of patients had hypercalcemia and 22% had hypercalciuria. Previous studies showed that approximately 30 to 50% of patients with sarcoidosis have hypercalciuria, and 10 to 20% have hypercalcemia.[15] Increased intestinal calcium absorption induced by high serum calcitriol concentrations (1,25-dihydroxyvitamin D) is the primary abnormality, although a calcitriol-induced increase in bone resorption may also contribute.[16]Hypercalcemia normally suppresses the release of PTH and therefore the production of calcitriol, but in sarcoidosis and other granulomatous diseases, activated mononuclear cells (particularly macrophages) in the lung and lymph nodes produce calcitriol from calcidiol independent of PTH.[17]

The other aspect of our study to be noted was that the most common symptoms of sarcoidosis were dyspnea and cough. In addition, the most common radiologic findings were micro and macro parenchymal nodules and traction bronchiectasis.[18] At high-resolution CT, the most typical findings of pulmonary involvements are micronodules with a perilymphatic distribution, fibrotic changes, and bilateral perihilar opacities. These findings could help clinicians to keep sarcoidosis in mind when encounter these symptoms and radiologic findings in a patient with refractory pulmonary symptoms.

Airway involvement exists in approximately 40% of patients with stage I disease, and approximately 70% of patients with stage II or III.[19] Airway involvement in sarcoidosis is manifested as mucosal erythema, oedema, granularity and cobblestoning. Cobblestoning of mucosal membrane in airways is also an important finding for clinicians that need specific attention by clinicians.[20]

In conclusion, sarcoidosis is a multi-organ disease with various features and ambiguous symptoms and non-specific radiologic findings. Pulmonary involvements are both fibrosis and granulomatosis and the most common manifestations are parenchymal nodues, bronchiectasia and high-grade fibrosis. The most common extra-pulmonary involvement is arthritis mostly in stage 1. Duration of disease had no correlation with stage or severity of disease or extra-pulmonary involvements. Lab tests are non-specific and have no correlation with duration or severity of disease. Future studies with long-term follow-ups should be designed to explore association of various findings and response to treatment.

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