

## Original Article

### **Five years experience of Sarcoidosis at a tertiary care centre in Pakistan**

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#### **Abstract**

**Objective:** To review the medical records of patients diagnosed with sarcoidosis for sociodemographic characteristics, clinical presentation, mode of diagnosis, and stage of disease at a tertiary care centre of Pakistan.

**Method:** The medical records of 47 patients consecutively diagnosed with sarcoidosis from 2003 to 2008 were reviewed retrospectively. The sociodemographic characteristics, clinical presentation, mode of diagnosis, organs involved, stage of disease and follow up were reviewed.

**Results:** Out of 47 patients, 26 (55%) were female and 21 male. Cough and shortness of breath were the main presenting symptoms. Mode of diagnosis was gallium scan in 27 patients, biopsy in 16 patients and High Resolution CT scan in 3 patients. Asymptomatic patients at presentation did not require any treatment and did well on follow up. Eighteen patients required steroid therapy which was slowly tapered off. Two patients required azathioprin in addition to steroids.

**Conclusion:** Sarcoidosis is a diagnostic challenge in countries where tuberculosis is endemic, however physicians still need to keep sarcoidosis in the differential diagnosis due to clinical, histological and radiological similarities between the two conditions (JPMA 60:293; 2010).

## Introduction

Sarcoidosis is an idiopathic, non-caseating, granulomatous systemic disease with protean clinical manifestations. The disease affects both sexes, all races and all ages. The highest prevalence rates are reported in Swedes, Danes and African Americans in USA. Sarcoidosis is rarely reported from Spain, Portugal, India, Saudi Arabia and South America.<sup>1</sup> Data from Pakistan is scanty and only one small case series described 43% prevalence of sarcoidosis among those with isolated mediastinal lymphadenopathy.<sup>2</sup> The exact etiology of Sarcoidosis has not yet been defined, but It has been suggested that infective agents, including mycobacteria, propionibacteria, parasites such as Schistosoma, and fungi such as Coccidioides, are likely triggers (but not as infection) in a genetically predisposed individual and that this initial event leads to the sarcoidosis granulomatous response.<sup>3</sup> Other agents such as beryllium, zirconium, and aluminum can also trigger the granulomatous response.<sup>3</sup>

The main diagnostic dilemma with sarcoidosis is in countries where tuberculosis is endemic because of clinical, histological and radiological similarities between the two diseases.

Sarcoidosis in Pakistan is emerging from obscurity and we are presenting, to our knowledge, the first case series of patients with sarcoidosis. In our current study, we evaluated the clinical and laboratory characteristics mortality and morbidity in 47 patients with sarcoidosis who were followed in our center from 2003 to 2008. The major goal was to investigate the sociodemographic characteristics, clinical presentation and symptoms and to determine the severity and prognosis of sarcoidosis in our region.

## Patients and Methods

Medical records of 57 patients diagnosed with sarcoidosis from over a five year time period from 2003 to 2008 at our center were reviewed retrospectively. All patients were seen at pulmonary outpatients or inpatients of Shaukat Khanum Memorial Cancer Hospital and Research Centre. The sociodemographic characteristics, clinical presentation, symptoms, mode of diagnosis and organ involved; stage of disease at the date of diagnosis, and follow up were reviewed. Pulmonary outpatient is a tertiary care service entertaining referrals from the various departments of our faculty or from outside physicians. Records of all patients diagnosed with sarcoidosis for the study period were reviewed initially to confirm the diagnosis of sarcoidosis. The medical records and when indicated, the radiographic findings of each person with a diagnosis of sarcoidosis were reviewed by the senior author. Forty seven patients were enrolled to analyze the sociodemographic characteristics, clinical presentation, symptoms, mode of diagnosis, organ involved; stage of disease at the date of diagnosis, and follow up. A diagnosis of

Sarcoidosis was made on the basis of either biopsy, high resolution CTscan or on the basis of gallium scan showing a bilateral lacrimal, parotid and mediastinal lymph node uptake "Panda" and "Lambda" signs. The date of last evaluation was the date of last clinical evaluation of the signs and symptoms of sarcoidosis in the outpatient clinic.

SPSS statistical package (SPSS version 17) was used for the analysis of the data. The means and the standard deviations for the continuous variables were calculated.

## Results

There were a total of 47 patients with Sarcoidosis. Of these 47 patients, 26 (55%) were female and 21 (47%) male. Mean age of presentation was  $42 \pm 12.7$  years. At presentation 7 (10.6%) patients were asymptomatic, 17 (36%) had cough, 15 (32%) had cough with shortness of breath, 3 had chest pain, 3 (6.4%) patients had red eye and chest pain and 4 patients (8.5%) had shortness of breath.

Mode of diagnosis was found to be Gallium scan in 28 patients with characteristic "panda" and "lambda" signs (59%). Sixteen (32%) patients underwent biopsy to reach diagnosis of sarcoidosis and 3 patients had characteristic High resolution CT scan findings leading to diagnosis of sarcoidosis.

Stage of disease was stage I in 17 (36.2 %) patients, stage II in 25 (53%) and stage III e in 5 (10%) patients. None of our patients had stage IV disease.

Regarding treatment, 27 (57.4%) patients were asymptomatic at presentation and were offered no treatment. Steroids were required in 18 patients and one patient each required Azathioprine with steroids and steroids with radiotherapy. The patient that required radiotherapy had Neurosarcoidosis with recurrent hydrocephalus and did not respond to steroids and Azathioprine.

Out of 47 patients, 37 (78%) remained on follow up. Patients who were asymptomatic at presentation continued to do well. Patients who needed steroids at presentation were tapered off steroids with resolution of symptoms except three patients who are still on steroids. One patient is currently on steroids and Azathioprine with no clinical symptoms. The only patient who did not do well, had Neurosarcoidosis.

## Discussion

Sarcoidosis is a non-caseating granulomatous disease of unknown etiology. The prevalence of sarcoidosis is estimated at 1-40 per 100 000 inhabitants.<sup>1</sup> It is seen throughout the world and affects all races, both sexes and all ages.<sup>1,3</sup> There are geographical and racial differences in the occurrence of sarcoidosis.<sup>1,4,5</sup> The disease shows a consistent predilection for adults less than 40 years age, with a peak in those 20 to 29 years age. In Scandinavian countries and Japan,

there is a second peak incidence in women more than 50 years of age.<sup>6</sup> In one review from Pakistan the peak incidence of age was found between 30 to 40 years age as compared to our review which showed a mean age of 42 years which is slightly higher as compared to trends around the world.<sup>7</sup> The annual incidence of sarcoidosis in Asians was found to be 16.8% in one retrospective survey of 156 patients attending two South London hospitals between 1969 and 1982 as compared to 1.5% for Caucasians.<sup>8</sup> Sarcoidosis is rarely reported in India, Spain, Saudi Arabia, or South America, partly because of the absence of mass screening programmes and also because of the more commonly recognized granulomatous diseases (tuberculosis, leprosy, fungal infection) that obscure the recognition of sarcoidosis.<sup>9,10</sup>

The exact etiology of sarcoidosis is unknown. Recent data suggests genetic inheritance, infectious transmission, and shared exposure to environmental agents as a possible cause. Infectious organisms such as viruses, mycobacteria, *Borrelia burgdorferi*, and *Propionibacterium acnes* have been implicated as potential causes of sarcoidosis. Environmental exposure to beryllium, aluminum, and zirconium can result in a granulomatous response similar to that of sarcoidosis. Current theory proposes, that the disease develops in genetically predetermined hosts who are exposed to certain environmental agents that trigger an exaggerated inflammatory immune response leading to granuloma formation.<sup>1</sup>

The characteristic lesion of sarcoidosis is a discrete, compact, noncaseating epithelioid cell granuloma.<sup>1</sup> The main diagnostic dilemma with sarcoidosis is in countries where tuberculosis is endemic. Due to pathological, clinical and radiological similarities of sarcoidosis with tuberculosis, patients receive multiple course of anti-mycobacterium therapies while lung damage continues to progress.<sup>11</sup> Most commonly sarcoid granulomas are seen in Lymph nodes (especially intrathoracic), lungs, liver, spleen, and skin, which are of a similar nature in all organs.<sup>12</sup> Prior studies clearly showed that clinical manifestation of sarcoidosis varies in different parts of the world but still respiratory symptoms are most common as compared to any other symptom as reported by Jerome and Johnson.<sup>13</sup> Cough and shortness of breath were the leading presenting symptoms (68%) of sarcoidosis patients at our centre. This cannot be commented on as our data was from the pulmonary outpatients. There was one patient with central nervous system disease.

Work up required for diagnosis of sarcoidosis must accomplish the following four goals: (1) Establish the diagnosis (2) assess the extent and severity of organ involvement, (3) assess whether the disease is stable or is likely to progress, and (4) determine if therapy will benefit the patient.<sup>1</sup> Mostly, sarcoidosis is diagnosed after excluding other varieties of granulomatous disorders like infections (e.g.

tuberculosis, histoplasmosis, coccidiomycosis, brucellosis), autoimmune disorders (e.g. Wegener's granulomatosis, Churg-Strauss vasculitis) and malignancies (e.g. lymphomas, carcinoma). Further important differential diagnoses include chronic beryllium disease, hypersensitivity to other metals/substances (titanium, aluminum, talc, etc.), exogenous-allergic alveolitis and drug induced pneumonitis (e.g. methotrexate).<sup>1,4,14</sup> Multi organ involvement increases the clinical likelihood of sarcoidosis.<sup>1</sup> The American Thoracic Society/American College of Chest Physicians/World Association of Sarcoidosis (ATS/ACCP) and Other Granulomatous Disorders statement on sarcoidosis proposes that the diagnosis is most secure when supported by tissue biopsy and trans-bronchial biopsy with four to five lung biopsies. This is also the recommended procedure. In most cases the diagnostic yield of Trans bronchial biopsy varies from 40 to 90 % depending upon the operator's experience.<sup>1,15,16</sup> The appearance of bilateral symmetrical uptake in Parotids and lacrimal glands "Panda" pattern combined with bilateral uptake in hilar and para tracheal lymph nodes, a "Lambda" pattern on a total body . 67Ga scan makes the diagnosis of sarcoidosis and obviates the need for invasive diagnostic procedures.<sup>2,17,18</sup> High resolution CT scan has established value not only in diagnosis but also in prognosis as well with characteristic nodular infiltrates with bronchovascular and sub pleural distribution, thickened interlobular septa, architectural distortion, and conglomerate masses originating from coalescence of nodules in the perihilar, peribronchovascular, or sub pleural regions.<sup>19</sup> Another imaging modality whole-body FDG PET scan is of value in detecting occult diagnostic biopsy sites in patients with sarcoidosis and in the assessment of residual activity in patients with fibrotic pulmonary sarcoidosis.<sup>20</sup> Patients with sarcoidosis require a chest x ray to define stage of disease as this has a prognostic implication.<sup>21</sup> Simultaneously full blood count, liver function test, calcium levels and electrocardiogram are also a part of work up of patients with sarcoidosis.<sup>22</sup> Raised angiotensin converting enzyme inhibitor level (ACE) can be seen in patients with sarcoidosis but this is non-specific and can be raised in a variety of disease.<sup>23</sup> Serum ACE has been used as a diagnostic test but has a low sensitivity (60%) and poor specificity, it cannot be used as part of the diagnostic algorithm.<sup>2</sup> Pulmonary function tests are not helpful in establishing the diagnosis. Current guidelines recommend measurement of Forced Expiratory volume (FEV1), Forced vital capacity (FVC) and Diffusion capacity (TLCO) routinely and to focus on variables that are most severely impaired or change the most at follow-up.<sup>22</sup> We followed the American thoracic society guidelines when investigating patients with sarcoidosis. Gallium scan was used with good results and around 28 patients had characteristic Gallium scan findings confirming the diagnosis. Non invasive

charm of Gallium scan along with ATS and ACCP recommendations, keep this diagnostic modality as a favoured option to confirm the diagnosis. Biopsy was also utilized in 16 patients and HRCT in 3 patients. The results were comparable with bench mark and evidence based American Thoracic Society guidelines.

Treatment of sarcoidosis is usually with steroids but symptoms and/or findings that necessitate corticosteroid therapy remain controversial. Systemic therapy is undoubtedly indicated for cardiac disease, neurologic disease, eye disease not responding to topical therapy, and hypercalcaemia. For pulmonary disease there are no clear cut indications. Spontaneous remission can occur in 55-90% of patients with stage I radiological disease, 40-70% with stage II disease and 10-20% with stage III disease.<sup>19,24,25</sup> Guidelines recommend that progressive and symptomatic intra-thoracic disease should be treated.<sup>1</sup> In patients not responding to steroids or with severe extra pulmonary disease like involvement of central nervous system, immunosuppressive therapy can be considered.<sup>22</sup> Immunosuppressive therapy has a role as steroid sparing agent and also as a treatment. Azathiopyrine, methotrexate, hydroxychloroquine and cyclophosphamide, have all shown some benefit in small case series, but a large randomized trial would be required to prove the steroid sparing potential and also for use as an alternative to steroids.<sup>22</sup>

We did not offer any treatment to our asymptomatic patients with sarcoidosis and kept them only on three monthly follow up and they did well. Symptomatic patients either with cough, shortness of breath or red eyes were given steroids, they showed generally good clinical and radiological improvement (except two patients) and steroids were gradually tapered off. They were currently doing well on follow up. The two patients who needed steroid sparing agents have not shown any signs of sarcoidosis relapse.

In our opinion, sarcoidosis may have been under diagnosed. Despite the high prevalence of tuberculosis, physicians need to keep sarcoidosis in their differential diagnosis in appropriate clinical and radiological settings. Further studies to determine the incidence, prevalence, presentation variation and prognosis for sarcoidosis in our population are required.

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