A review of pulmonary sarcoidosis

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Sarcoidosis is an inflammatory disease of unknown aetiology that affects multiple organs, with a predilection for the respiratory system. The defining characteristic is the presence of non-caseating granulomas on histopathology. It is a disease that can mimic several infectious and non-infectious disorders, and implementation of treatment is often delayed if the diagnosis is not suspected.


History and evolution

Jonathan Hutchinson initially described sarcoidosis as 'Mortimers malady' in 1869, and thought it to be a dermatological condition after reviewing two patients who had multiple plaques on their body, which differed from tuberculosis (TB) and systemic lupus erythematosus. A French dermatologist, Besnier, then coined the term 'lupus pernio' several years later after describing a patient with purplish swellings on the nose, ears and fingers. At the turn of the 20th century the term 'sarcoid' was conceived after the Norwegian dermatologist, Caesar Boeck, thought the lesions resembled benign sarcoma. He was the first physician to demonstrate the granulomas on histology as well as highlight the multisystem nature of the disease. The disease's multisystem nature became more apparent with the classification of two distinct syndromes: Heerfordt syndrome, which was characterised by cutaneous lesions, uveitis, parotid and submaxillary salivary gland enlargement and cranial nerve palsies; and Löfgren syndrome, which was characterised by fever, bilateral hilar lymphadenopathy, polyarthritis and erythema nodosum.[1] The disease was then proven by a test developed by Angsar Kveim that was improved by Louis Siltzbach and is therefore known as the Kveim-Siltzbach test.[1] It involves injecting crude pieces of sarcoid tissue intradermally which results in papules several weeks later in patients with sarcoidosis, but not in controls.[2]

Epidemiology

The incidence of the disease in the northern hemisphere is 5 - 40 per 100 000. The disease is almost 4-fold more likely to affect African Americans compared with white Americans. The disease also tends to affect females in a 2:1 ratio compared with males.[3,4] It occurs in the 2nd and 3rd decade of life, however, studies in Scandinavia have demonstrated a bimodal peak with the disease also occurring in the 4th to 6th decade.[5] It has also been demonstrated that African Americans have a later age of onset, being affected in the 4th decade.[4] A few studies have been conducted in South Africa (SA), albeit on a small series and have demonstrated similar findings with predominance in Africans.

However, Benatar et al.[6] reported conflicting data from a study in Cape Town, which showed a 1:1 female to male ratio in black Africans; however, it should be noted that they had a total of 25 black African patients in the study. A study conducted in Johannesburg by Smith et al.[7] showed a ratio of 1:1 in the white population. Morar et al.[8] showed a preponderance among Africans by race and among females by gender.

Aetiology and pathogenesis

The aetiology of the disease is ever-evolving and still not well understood. It is an interplay of genetic, environmental, host immunological and, possibly, infectious factors. The hypothesis on the development of the granuloma is that it is due to an exaggerated inflammatory response to a partially soluble or insoluble antigen which walls off the agent resulting in granuloma formation. This probably occurs to prevent injury to the surrounding tissue.[9] The granulomas are composed of tissue macrophages, activated monocytes, T and B lymphocytes, fibroblasts, and other matrix-associated cells.

There is a 5-fold increased risk of sarcoidosis among first-degree relatives and it was also shown that there is a higher concordance rate among monozygotic compared with dizygotic twins.[10,11] There are also certain major histocompatibility complexes associated with specific phenotypes with different human leukocyte antigen genes between acute, chronic active, remitting and extra pulmonary sarcoidosis.[12,13] Sarcoidosis has shown seasonal clustering, with more incident cases in the latter part of winter and the beginning of spring in both the northern and southern hemispheres.[14] The disease is more prevalent in certain occupations, with a higher incidence in military and agricultural workers.[15] It was noted that there was a higher incidence of sarcoidosis among first responders to the 2001 World Trade Centre attacks in New York City.[16] It is intriguing to note that smoking is a protective factor against sarcoidosis.[17]

The role of infection is not as well understood in the pathogenesis and aetiology. A study in Japan had revealed the presence of *Propionobacterium acnes* in a small proportion of patients with lung and lymph node biopsies, but it is now thought to be a latent organism.[18] There is no overt link between *Mycobacterium tuberculosis* and sarcoidosis, however, *Mycobacterium genes, such as* protein mycobacterial catalase-peroxidase (*mKatG*), have been found in sarcoid samples which had identical physicochemical
properties to the Kveim–Siltzbach reagent and which induced a similar T cell response.[19]

**Pulmonary sarcoidosis**

The lung is the most commonly affected organ in sarcoidosis, with ~90 - 95% of cases having pulmonary involvement; in 50% of cases the index manifestations are pulmonary in nature.[20,21] The presentation is protean and varies from asymptomatic to cough, dyspnoea, fatigue and wheezing.[15,21,22] The presence of wheezing is generally due to bronchial hyper-reactivity and it becomes difficult to differentiate it from asthma, hence sarcoid may be misclassified as asthma or bronchitis.[23] Clinical examination also depends on the stage of the disease, and ranges from normal to features of chronic lung disease at the end stages. Crepitations are evident in 4% of cases in early sarcoid and in 25% of cases who have end-stage disease.[24,25] Clubbing is uncommon; however, it may be present in those patients who develop bronchiectasis. Haemoptysis is also an uncommon symptom and if present, the exclusion of concomitant infections, malignancies and mycetomas is mandatory.[24] Pulmonary hypertension can occur in sarcoidosis for several reasons, including hypoxia, invasion of the pulmonary vasculature by granulomas, fibrocystic lung disease causing traction of the vessels, and pulmonary venous hypertension due to cardiomyopathy.[27] Pleural effusions and pneumothorax are rare presentations of sarcoid.[24]

Sarcoidosis tends to affect the upper lobes but can occur throughout the entire lung. Lesions can occur in the sub-pleural area and along the bronchial tree. The granuloma lesions have a predilection for the bronchovascular bundles and perilymphatic areas.[29–31]

Diagnosis is often delayed when there are only pulmonary symptoms present and generally requires assessment by multiple physicians before the diagnosis is made. In general, the diagnosis is made 3 months after the initial symptoms are noted and in 25% of patients it takes approximately 6 months before a diagnosis is established.[21,22] Diagnosis of sarcoid is based on clinical, radiological and histological features – histology is required to clinch the diagnosis based on the finding of the non-necrotising granulomas.[23,25] The only occasions when a biopsy is not required is for Heerfordt syndrome and Löfgren’s syndrome.[34] However, there are several conditions which can produce granulomas; hence the combination of clinical and radiological testing is required to establish the diagnosis. It is essential to exclude tuberculosis, which can mimic sarcoid and hence delay the diagnosis especially in the SA setting.

Radiological evaluation is still based on the chest X-ray (CXR) classification developed by Scadding in the 1960s, which categorises changes from stages 0 - 4 (Table 1).[19] This classification is very useful for staging patients and providing prognostic information, lower stages having a better prognosis compared to those in the higher category.

High resolution computed tomography (HRCT) of the chest is superior to CXR in detecting parenchymal disease and for evaluation of the mediastinum. It is useful for assessing if there is any other concomitant lung disease as well as assessing if there is disease reversibility.[36,37] The HRCT also assists in identifying the most suitable area for biopsy if it is indicated.[37,38] The indication for an HRCT is when there is a high index of suspicion but the CXR is atypical or discordant with the clinical findings. There are several features which are suggestive of sarcoidosis but not pathognomonic of the disease. These features include: beading along the fissures and pleura; lymph node calcifications; paraseptal nodules in the upper lobe; traction bronchiectasis; honeycombing; air trapping on expiratory phase; and relative sparing of the lower lobes.[30,34]

[18F]-Fluorodeoxyglucose positron emission tomography ([18F]FDG-PET) is a useful test in ascertaining disease activity. It is useful for identifying organ involvement as well as areas of maximal disease activity. This is specifically helpful in identifying areas for biopsy for histological diagnosis as biopsies from lesions that are more metabolically active produce a far greater diagnostic yield compared with inactive lesions. The [18F]FDG-PET also aids the diagnosis in cases with persistent symptoms where the conventional biomarkers are not supportive, as it may demonstrate ongoing disease activity. A drawback of the [18F]FDG-PET is the cost, high radiation exposure and the time taken to conduct the test.[22,34,39,40]

Magnetic resonance imaging is not useful for pulmonary disease. Its main role is for the detection of cardiac and neurological disease.[22,23] Gallium scanning has also fallen away in recent years owing to the development of more specialised diagnostic tools. It has a low specificity and is not easily reproducible.[19,30] There is no clear-cut definition of what constitutes the amount of abnormal signal needed to determine active disease.

Bronchoscopy is a useful tool in the diagnosis of sarcoid as it allows for visual inspection, bronchoalveolar lavage (BAL) and biopsy. On inspection, cobblestoning of the endobronchial mucosa can be noted owing to the presence of multiple waxy nodules. There can also be mucosal thickening, which results in the loss of normal contours of the spurs at the level of bifurcation of the bronchi. Bronchial stenosis can occur although it is extremely rare and it may be confused with a malignancy.[21]

BAL fluid cytology can assist in the diagnosis of sarcoid; however, it is not routinely used in the SA setting. There is usually a lymphocytic predominance with a normal eosinophil and neutrophil count.[41] A lymphocyte count of >25% after the exclusion of infection is highly suggestive of sarcoidosis.[21] There was a suggestion to use the CD4/CD8 ratio; however, it remains controversial as it has a very low sensitivity and high specificity when the ratio is above 3.5.[42] Endobronchial and transbronchial needle aspiration, with or without endobronchial ultrasound, is very useful for histological confirmation of sarcoid. The yield of granulomas detected on endobronchial biopsy is higher if there is an abnormal macroscopic appearance (90%) compared with a normal appearance (40%).[24]

### Table 1. Scadding staging based on CXR

<table>
<thead>
<tr>
<th>Stage</th>
<th>CXR</th>
<th>Resolution, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Bilateral hilar lymphadenopathy</td>
<td>60 - 90</td>
</tr>
<tr>
<td>2</td>
<td>Bilateral hilar lymphadenopathy with pulmonary disease</td>
<td>40 - 70</td>
</tr>
<tr>
<td>3</td>
<td>Pulmonary disease without bilateral hilar lymphadenopathy</td>
<td>10 - 20</td>
</tr>
<tr>
<td>4</td>
<td>Lung fibrosis</td>
<td>0</td>
</tr>
</tbody>
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CXR = chest X-ray.
Transbronchial biopsy yields ~40 - 90%; however, it carries a higher risk of pneumothorax and the risk of sampling the incorrect area.[15] Endobronchial ultrasound fine-needle aspiration and transbronchial needle aspiration is very useful in patients who have mediastinal adenopathy with a yield rate of 70 - 90%. It has now virtually replaced mediastinoscopy for lymph-node evaluation.[14,15,44]

Several biomarkers have been developed to assist in the diagnosis and response to treatment for sarcoidosis; however, the most widely used in our setting still remains the serum angiotensin-converting enzyme (sACE) that is produced by the cells surrounding the granuloma. It has a sensitivity of 60% and a specificity of 70% and is elevated in 40 - 80% of patients with sarcoidosis.[16] It has a high false-positive rate and is elevated in other granulomatous and non-granulomatous diseases.[16] It is reliable for monitoring disease activity and response to treatment but not for establishing the diagnosis.[33] At present, even with the newer biomarkers, there is no single biomarker that can be reliably used to diagnose, monitor disease activity or make treatment decisions.

Pulmonary function testing (PFT) is useful for monitoring the response to treatment in patients with pulmonary sarcoidosis. The majority of patients have a restrictive pattern on spirometry; however, a significant proportion of patients have an obstructive pattern.[15,38] The obstructive pattern may be due to narrowing from fibrosis, granuloma infiltration, small-airway disease or compression by mediastinal lymph nodes.[21] Obstructive PFT is more common in those with progressive parenchymal disease.[47] The greater the disease progression, the more likely of having an impaired PFT.[34] The most common finding is a reduced lung volume with a reduction of the forced vital capacity (FVC).[21] It is also the most simple and accurate parameter to reflect the impact of pulmonary disease, hence making it a good parameter for follow-up and treatment response.[21]

There is also a reduction in the membrane component of the diffusion capacity for carbon monoxide which is a very sensitive test.[15] The 6-minute walk test is only helpful in assessing the functional status of patients with sarcoid and is typically reduced. It is further reduced in those with concomitant pulmonary hypertension.[39]

It is mandatory to perform other baseline tests as sarcoid is a multisystem disease. A screening electrocardiogram for cardiac sarcoidosis, an ophthalmological exam for eye involvement, a liver function test for hepatic disease, urea and electrolytes, as well as serum and urinary calcium, are all necessary, as sarcoid is a known to cause hypercalcaemia and the complications that arise from it.

Sarcoidosis treatment requires immunosuppressive therapy with the aim of preventing organ damage, improving symptomatology as well as quality of life and to induce remission.[44] Many patients will resolve spontaneously without treatment although a relapse may occur. Therapy is indicated in those who are symptomatic, have parenchymal disease, progressive disease and those with marked disease activity.[40,56]

The choice of immunosuppressive agent is influenced by several factors. Glucocorticoids are favoured in patients who would respond well, have no comorbidities such as diabetes mellitus and hypertension, and acute onset disease.[49] Steroid-sparing agents are used in those who are resistant to glucocorticoids, have comorbidities and who have extrapulmonary involvement, such as concomitant cardiac and neurosarcoidosis.[49,56]

Glucocorticoids have been the mainstay of treatment as they are readily available, reliable, effective, easily titrated and are cheap relative to the steroid-sparing agents. There is marked improvement in radiological and PFT parameters in patients who receive steroids. There is no data to determine the starting dose, nor is there any evidence of when and how to start weaning the steroids as well as the ideal treatment duration.[15,22,49,50] Expert opinion suggests a starting dose of 20 - 40 mg/day for 1 - 3 months, then to taper down over the next 3 months to 10 - 15 mg/day, or the lowest effective dose, and maintain that dose for a further 9 - 12 months, with the total treatment duration being between 12 and 18 months.[20] Tapering should not be too rapid as this may cause relapse. Intravenous glucocorticoids have been used and their only benefit has been shown to be quicker remission, however, the clinical status at 1 year has been the same as in those who received oral treatment.[50]

Cytoxic agents are used in those who fail to respond adequately to glucocorticoids and in those in whom glucocorticoids are contraindicated. The most commonly used second-line agent is methotrexate.[48,50] It is administered orally or via a transdermal patch at a weekly dose of 10 - 20 mg. It tends to have a long response time and it may take up to 6 months to see tangible results.[21]

There has been limited case series reporting the use of azathioprine as a second-line agent for sarcoid. It is administered at a daily dose of 1.5 - 2.5 mg/kg. It has a higher risk of infections as well as greater side effects when compared with methotrexate[49] and can be considered in those in whom fertility is required.

Leflunomide is another drug of choice as a steroid-sparing agent, however, there are minimal data on its use. It is administered at a daily dose of 10 - 20 mg and has less pulmonary toxicity compared with methotrexate.[50]

Mycophenolate mofetil can also be used for the treatment of sarcoidosis but the available data are limited to case reports. The dose is 500 - 1 500mg daily and it has a side-effect profile which can be very limiting.[49,50,52]

In patients with very severe sarcoidosis in whom there is minimal or no response with the anti-metabolite agents mentioned above, the use of monoclonal antibodies can be considered; however, the evidence to support their use is based on case reports of small numbers of patients and limited series data – infliximab is an exception as it has undergone randomised control trials and has shown some benefits in the treatment of pulmonary sarcoid.[49,50,52,54]

The assessment of the response to treatment is based on several factors, i.e. improvement in symptoms, radiological improvement, and an improvement of >10% in the FVC on PFT. Poorer responses have been noted in cases with involvement of ≥3 organ systems, advanced respiratory disease and in African Americans.[49,50]

Sarcoidosis and HIV can coexist and this is important in the SA setting. Studies in Europe have revealed that patients who are severely immunosuppressed do not develop sarcoidosis but those patients who commence highly active antiretroviral therapy and who achieved viral suppression, were more likely to develop sarcoidosis. This has given rise to the postulation that it may develop due to an immune reconstitution inflammatory syndrome.[55,56]

**Conclusion**

Pulmonary sarcoidosis remains a challenge for physicians to diagnose and treat optimally as it can mimic several other diseases. The
management guidelines are based merely on expert opinion. Owing to the high burden of HIV and TB, and its impact on pulmonary sarcoid, as well as the fact that we have a multiracial population, further research is required in the SA setting to better ascertain the epidemiology of the disease.


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