Sarcoidosis: Current Concepts of Pathogenesis and Treatment

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Sarcoidosis is a common systemic granulomatous disease. Diagnosis depends on the histological finding of non-caseating granulomas and the exclusion of other causes of such pathology. Although the aetiology of this disease remains unknown, recent insights into its pathogenesis have been gained through studies on both the systemic and the pulmonary immune response in patients with this disease. It is clearly an immunologically mediated disease, where granuloma formation and fibrosis depend on a complex interaction among activated macrophages and helper T cells, an interaction that appears to be mediated by cytokines. Not all patients with sarcoidosis require treatment, though in those who do, corticosteroids remain the mainstay of therapy.

Sarcoidosis is an enigmatic disease; a multisystem granulomatous disorder which principally involves the lungs, skin and reticulo-endothelial system, but which has the capacity to involve almost any organ to varying degrees. The distinctive nature of the granulomatous lesions led to its recognition as a specific clinical entity over 100 years ago by Boeck, but despite an improved understanding of its pathogenesis, the cause of sarcoidosis remains as much a mystery in the last decade of the twentieth century as it was when it was first described.

Epidemiology
While sarcoidosis is a common disease world-wide, its true prevalence is difficult to assess, both because of its marked geographic and racial variation, and the variability of its clinical presentation. Epidemiological studies have been undertaken using a variety of different methodologies, and estimates of disease prevalence tend to reflect the method used.

Because sarcoidosis is often asymptomatic, radiographic studies have been widely used as a screening method, though difficulty can be experienced in interpreting chest X-rays in countries where tuberculosis is common. Using this method, the prevalence of sarcoidosis has been found to vary from 64 per 100,000 people in Sweden to less than 10 per 100,000 in Canada, and an annual incidence of 8 per 100,000 in Denmark. In general, the disease is detected two to four times more frequently using radiographic methods than when relying on clinical detection.

Autopsy studies have also been used as a method for more precisely determining the prevalence of this disease. In Sweden, one such study revealed...
sarcoidosis in 42 of 6706 post-mortem cases, giving a prevalence rate ten times higher than that ascertained by mass radiographic screening. Thus data from several careful studies carried out in the Scandinavian countries have revealed an incidence and prevalence of sarcoidosis considerably higher than would be expected based on clinical cases.

While there is confusion as to the true prevalence of the disease, there is no doubt that sarcoidosis is a disease of young people, with a peak incidence between 20 and 34 years of age. The disease is up to 14 times more common in the Black population than amongst Whites, and this holds true in both the USA and South Africa. Other racial and ethnic groups, such as Puerto Rican residents in New York and Irish immigrants to the UK also show a particularly high incidence of sarcoidosis. Although the male to female ratio is about equal in most White populations, Black females in the USA develop sarcoidosis twice as frequently as their male counterparts.

The tendency for familial aggregations in this disease has suggested that genetic factors may play a role in its pathogenesis, although this remains ill defined, and may well represent the effects of environmental agents.

Aetiology
The aetiology of sarcoidosis is unknown. It has long been suggested that one or more environmental agents may initiate the disease, and suspicion has been cast upon a variety of microorganisms, pollens, and other exogenous materials, though there is no clear-cut evidence implicating any of these. Similarly, the mode of entry of the provoking agent remains unknown, though inhalation, ingestion or dermal contact have all been postulated.

Pathogenesis
The characteristic lesion of sarcoidosis is a non-caseating granuloma composed of macrophages, epithelioid cells, lymphocytes and giant cells. There is no associated central necrosis, the cuff of lymphocytes that surrounds the granuloma is often relatively insignificant when compared with that seen in tuberculosis and other granulomatous diseases, and the granulomas are often surrounded by fibrosis. Clearly, alterations in the normal function of lymphocytes, monocytes, and avascular macrophages and fibroblasts are central to the development of the disease.

Studies of bronchoalveolar lavage fluid have resulted in new insights into the pathogenesis of sarcoidosis, by enabling a closer examination of the state of activation of the various cellular components during the course of the disease (Fig. 1). Early in the course of pulmonary sarcoidosis there is a marked inflammatory response in the alveolar walls, with little granuloma formation or fibrosis. It has been suggested that this represents the first stage in the development of the disease, and that critical alterations in cellular function at this stage may underpin the granuloma formation and fibrosis that characterizes the later stages of the disease.

Studies on lavage fluid obtained during this phase show that helper/inducer T (CD4+) lymphocytes are prominent cells, and that these T cells are immunologically activated. They are capable of producing a variety of cytokines which are believed to play an important role in the formation of granulomas, through attraction and activation of monocytes and alveolar macrophages. Similarly, the alveolar macrophages which are present within lavage fluid and in lung biopsies are also activated, and have been shown to secrete a number of lymphokines, including interleukin-1 (IL-1), and also to express HLA Class II antigens on their surface. Such macrophages provide a potent stimulus for further recruitment of T cells. Thus it has been postulated that the sarcoïd granuloma is a result of the interaction between T cells and macrophages that occurs within the lung, an interaction mediated and modulated by the secretion of cytokines. The state of activation of alveolar macrophages may be mediated by the balance between helper and suppressor T cells within the alveolar wall, with activation of macrophages being favoured by an excess of alveolar helper T cells. Activation of macrophages under the influence of cytokines may result in their morphological and functional differentiation, and result in the formation of epithelioid cells and giant cells that characterize the disease. Certain cytokines such as interleukin-3 have been shown to activate macrophages and promote their fusion to form giant cells.

During the course of the disease, the most striking pathological change in the lung is the development of fibrosis, which in turn is responsible for the most significant clinical manifestations of sarcoidosis. This fibrosis may be a result of the persistence of inflammation in the lung parenchyma, with the activated macrophages releasing factors which stimulate fibroblast chemotaxis, proliferation and collagen production. Factors such as IL-1, the fibroblast growth factors and fibronectin are probably important in this regard.

One of the major paradoxes in the pathology of sarcoidosis is the observation of a depressed systemic immune response despite evidence of an active cellular immune response within affected tissues. Studies of peripheral blood in patients with sarcoidosis commonly demonstrate a lymphopenia with a relative decrease in the helper T cell (CD4+) population. There is normally a predominance
Figure 1. The pathogenesis of pulmonary sarcoidosis (after Benatar). This diagram depicts the central role of alveolar macrophages and T-helper lymphocytes in the pathogenesis of sarcoidosis, and the possible role of cytokines in mediating these changes. Abbreviations: IL (interleukins), γ-INF (gamma-interferon), TNF (tumour necrosis factor), CSF (colony stimulating factors), FGF (fibroblast growth factors), Fn (fibronectin), PDGF (platelet-derived growth factor), EGF (epidermal growth factor), Coll (collagen).

of helper T cell in the peripheral blood leading to a helper/suppressor ratio of approximately two to one, but in patients with active sarcoidosis this ratio may be reversed. It has been suggested that this represents migration of CD4+ T cells from the circulation to the site of inflammation in the lung.4 Depressed delayed type hypersensitive skin responses producing cutaneous anergy is also a typical feature of active sarcoidosis.24

In contrast to depressed cellular immunity, humoral immunity is usually increased in activity in the peripheral blood of patients with active sarcoidosis, with a polyclonal increase in serum immunoglobulin25,26 levels being common. Immunoglobulin levels are also increased in bronchoalveolar lavage fluid, and it is possible that the increased immunoglobulin production occurs at the site of tissue inflammation, which is predominantly in the lungs. This is supported by the observation of an increase in the number of immunoglobulin-producing plasma cells in the lavage fluid of patients with active sarcoidosis, and the fact that this increase correlates with increased IgG levels in both lavage fluid and serum.26,27

The levels of specific antibodies directed against a variety of viral antigens, as well as autoantibodies directed against self-antigens, are elevated in the serum of patients with sarcoidosis.14,28 The exact pathogenetic role of these specific antibodies, and indeed of the heightened humoral immune response in general, remains unknown. Recent evidence indicates that B cell differentiation, proliferation and immunoglobulin synthesis is under the control of helper T cells. Such activated T cells secrete a variety of cytokines, such as IL-2, IL-4, IL-6 and gamma-interferon (γ-INF), that regulate B cell activity. Macrophages may also activate B cell activity by the secretion of cytokines such as IL-1 and tumour necrosis factor (TNF). Thus the increased activity of B cells seen in patients with
sarcoïdosis may be the result of increased cytokine secretion by activated macrophages and T cells.39

Clinical Features
Although patients with systemic sarcoïdosis may present with a variety of manifestations these can be divided conveniently into one of three groups. The first group includes those patients who are brought to clinical attention as a result of an abnormal chest X-ray or other laboratory anomalies. The second group comprise those presenting with symptoms of pulmonary involvement and the third group manifests extrathoracic disease. The clinical features of sarcoïdosis are outlined in Table 1.35

Asymptomatic disease
Roentographic screening studies indicate that asymptomatic sarcoïdosis is the most common form of this illness.3 Asymptomatic patients may be brought to clinical attention not only as a result of an abnormality in a routine chest X-ray, but also because of alterations in liver function tests, serum calcium, serum immunoglobulin levels, or in the cell mediated immune response. If the chest X-ray is abnormal, bilateral hilar lymphadenopathy is the most common manifestation (Fig. 2), as patients with interstitial disease are more likely to be symptomatic of their disease. Not surprisingly, the development of persistent symptomatic sarcoïdosis in this group is less common than those who initially present because of symptomatic disease.30

Pulmonary manifestations
Pulmonary symptoms are the most common manifestation of sarcoïdosis, being the presenting symptom in 30-60% of patients.31 Common respiratory symptoms include non-productive cough, chest pain, dyspnoea, haemoptysis and pneumothorax.

Abnormal chest X-rays are observed in most patients with sarcoïdosis.32,34 Radiographic findings in patients with this disease have been classified according to the presence or absence of hilar lymphadenopathy and pulmonary infiltrates, as outlined in Table 2.33 The Type I chest X-ray abnormality is the most common, with marked asymmetry of hilar nodes being unusual and suggesting the possibility of lymphoma or tuberculosis.6 Thoracic CT scanning may reveal lymphadenopathy not recognized on chest X-ray.34 Although hilar lymphadenopathy is the most common radiographic finding in patients with sarcoïdosis, pulmonary infiltration is the most significant clinical lesion, and is more likely to be seen in symptomatic patients. Infiltrative lesions may take the form of fine interstitial markings, coarse reticulonodular lesions, or confluent cotton wool infiltrates. Such infiltrates are most frequently observed in peribronchial and subpleural areas of the lung, and are often more extensive than they would be suggested by the patients’ symptoms. Other pulmonary features that may be observed on

<table>
<thead>
<tr>
<th>Type</th>
<th>Radiographic findings</th>
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<tbody>
<tr>
<td>0</td>
<td>Normal chest X-ray</td>
</tr>
<tr>
<td>I</td>
<td>Bilateral hilar lymphadenopathy</td>
</tr>
<tr>
<td>II</td>
<td>Bilateral hilar lymphadenopathy with pulmonary infiltrates</td>
</tr>
<tr>
<td>III</td>
<td>Pulmonary infiltrates in the absence of hilar lymphadenopathy</td>
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Table 2
Radiographic classification of pulmonary sarcoïdosis

Table 1
The clinical features of sarcoïdosis

<table>
<thead>
<tr>
<th>Pulmonary (%)</th>
<th>Extra-pulmonary (%)</th>
<th>Systemic (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough 30</td>
<td>Lymphadenopathy 73</td>
<td>Weight 28</td>
</tr>
<tr>
<td>Dyspnoea 28</td>
<td>Skin lesions 32</td>
<td>Fatigue 27</td>
</tr>
<tr>
<td>Chest pain 15</td>
<td>Liver disease 21</td>
<td>Fever 17</td>
</tr>
<tr>
<td>Sputum 11</td>
<td>Eye disease 21</td>
<td>Malaise 15</td>
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<tr>
<td>Haemoptysis 4</td>
<td>Erythema 8</td>
<td>Weakness 7</td>
</tr>
<tr>
<td></td>
<td>nodosum</td>
<td>Arthritis 6</td>
</tr>
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From Refs 35, 36.
chest X-ray include pulmonary fibrosis, bullous emphysema, pneumothorax and mycetomas.

Extrathoracic sarcoidosis
While sarcoidosis usually involves the lung and mediastinal nodes, it is a true multisystem disorder, and as such is capable of involving almost all other organs to variable degrees. While granulomatous inflammation can occur commonly in the skin, peripheral lymph nodes, eyes, liver, spleen, joints, bones and heart, involvement of any organ is possible.

Peripheral lymphadenopathy is the most common extrapulmonary clinical manifestation of sarcoidosis. Such lymphadenopathy is often associated with mediastinal lymph node involvement as well and occurs in some 75% of patients. Firm, non-tender lymphadenopathy is most commonly observed in the neck, although involvement of nodes in the axillary, epitrochlear, inguinal and femoral regions is also common. Because the histological appearance is so distinctive, biopsy of an involved lymph node is the most useful diagnostic procedure in patients with sarcoidosis.

The typical histological appearance of an involved lymph node is shown in Fig. 3. There is often a tendency for involved lymph nodes to undergo a gradual regression over a period of months to years.

Although a large number of infiltrative and plaque-like skin lesions are observed in patients with sarcoidosis the most common and typical clinical manifestation is erythema nodosum. These appear as tender red nodules 1–3 cm in diameter, commonly occurring on the anterior aspect of the leg. They represent a panniculitis (Fig. 4), an inflammation of the subcutaneous connective tissue septa due to vasculitis, and are often associated with arthritis and hilar lymphadenopathy in young females. Spontaneous regression of both the skin and pulmonary lesions is fortunately common in this situation.

Ocular disease is an important feature of sarcoidosis and is observed in about a quarter of patients in most large series. Ocular involvement may take the form of anterior or posterior
uveitis, kerato-conjunctivitis sicca, glaucoma, optic neuritis or retinal vasculitis. Lacrimal gland enlargement is seen in a small percentage of patients, and conjunctival granuloma are often seen. The most serious ocular manifestation of sarcoidosis is posterior uveitis, occurring in 8% of patients in one study. It often leads to significant visual loss, with glaucoma and cataract formation as frequent complications.

Abnormal liver function tests or hepatomegaly are observed in some 20% of patients with chronic sarcoidosis. The most frequent finding on liver function tests is elevated alkaline phosphatase and γ-glutamyl-transferase (GGT). Rarely patients may develop a picture of intrahepatic cholestasis with jaundice and pruritus. This varied clinical involvement is reflected in the pathological features of hepatic sarcoidosis, which ranges from an occasional granuloma to a chronic active granulomatous hepatitis, and on occasions cirrhosis, with the development of portal hypertension. The finding of granulomas on liver biopsy is very common in patients with sarcoidosis.37

Other common organs involved in sarcoidosis include the spleen, with clinically apparent splenomegaly occurring in 20–30% of patients, cystic bone lesions in 14% and arthritis, often associated with erythema nodosum, in a small percentage. A number of central nervous system abnormalities may be detected in patients with sarcoidosis38 and myocardial involvement is increasingly recognized.39 Hypercalcaemia and hypercalcuria, found in 17% of patients in Maycock's study,31 is the result of an increased production of 1-25 dihydroxycholecalciferol from sarcoid granuloma, which in turn increases the absorption of calcium from the gut.40,41 Corticosteroid therapy arrests the production of this vitamin and rapidly decreases the calcium level.

Investigations
The diagnosis of sarcoidosis depends on the finding of typical clinical manifestations supported by biopsy evidence of non-caseating granulomata and the exclusion of other granulomatous diseases. Tissue biopsy is thus important in the diagnosis of sarcoidosis, although not always clinically essential. Young patients presenting with asymptomatic bilateral hilar lymphadenopathy found on chest X-ray are likely to have sarcoidosis on clinical grounds, but even in this situation it may be necessary to biopsy a lymph node to exclude the presence of lymphoma.

It should be noted that the histological finding of non-caseating granulomata occurs in a variety of diseases, including mycobacterial and fungal infections, brucellosis, lymphoma and carcinoma, hypersensitivity pneumonitis, primary biliary cirrhosis and lymphomatoid granulomatosis. It is imperative that these differential diagnoses be excluded by careful history, physical examinations and appropriate laboratory investigations, and biopsy tissue should not only be appropriately stained but also cultured to exclude the presence of mycobacterial and fungal infections.

In determining the most appropriate site of biopsy, it is important to attempt to biopsy easily accessible organs that have obvious involvement. Often skin and superficial lymph nodes are available and should be biopsied in preference to more invasive procedures. In the absence of skin or lymph node lesions, trans-bronchial biopsy using a flexible fibreoptic bronchoscope is most frequently performed, and reveals typical sarcoid lesion in over 50% of patients. Higher yields are obtained in patients with Type 2 chest X-ray changes than in those with Type 1 and Type 3 lesions. Multiple biopsies should be obtained in order to maximize the chance of a positive sample. It is important during the initial clinical assessment to evaluate carefully all potential organ systems that may be involved by sarcoidosis.

Assessment of pulmonary function is important in evaluating patients presenting with early sarcoidosis, as well as in monitoring disease progression. This may be achieved by simple spirometry, which usually demonstrates a restrictive picture, though on occasions an obstructive Airways pattern may be noted, particularly in the late stages of the disease.

Whilst bronchoalveolar lavage has provided a great insight into the pathogenesis of sarcoidosis it is not a diagnostic procedure, and the finding of profuse alveolar lymphocytes and macrophages cannot be used to predict the outcome of the disease or treatment response.42,43

The assessment of disease activity is a vexed issue in the management of patients with sarcoidosis. Serial bronchoalveolar lavages, gallium scans44 and angiotensin converting enzyme measurements45 have been suggested as convenient measures of disease activity. However, recent studies suggest that these laboratory parameters are not sensitive and do not allow clinical decisions to be made. Turner-Warwick evaluated disease activity using a combination of bronchoalveolar lavage, angiotensin converting enzyme and gallium scans, and found no improvement in predicting clinical outcomes than when using chest radiographs.42 However, where there is persistent elevation of BAL lymphocyte counts for 12 months after disease onset, it is likely that the disease will fail to resolve spontaneously over the next 12 months.47 Alterations in T4/T8 cell ratios may also yet prove to be of some predictive value.46

Present evidence suggests that disease activity is best assessed by a combination of clinical
observations, chest X-rays and simple assessments of organ function.

**Indications for Treatment**

Not all patients with sarcoidosis require treatment, and careful clinical and laboratory assessment is important in evaluating the need to instigate therapy. The most common indications for therapy include: symptomatic pulmonary disease, uveitis, hypercalcaemia, hepatic disease, myocardial involvement and the manifestations of systemic disease, such as weight loss, night sweats and fever.

Corticosteroids remain the mainstay of therapy for patients with sarcoidosis and guidelines for the use of corticosteroids have been outlined which emphasize the need for careful monitoring of patients, use of the minimal effective steroid dose and the minimization of steroid side-effects. The response to steroid therapy depends on the chronicity and the extent of the disease, and prolonged corticosteroid therapy may be required in over half of the patients with sarcoidosis.\(^{14}\) While relapse occurs in up to half of all treated cases, it is unusual with steroid dosages greater than 15 mg/day. In patients requiring prolonged high dose corticosteroid therapy consideration should be given to the use of alternative drugs or steroid sparing therapy. Cyclosporin has recently been reported to be of benefit in patients with sarcoidosis, and similarly methotrexate may be of value, especially in patients with severe skin involvement. Antimalarials such as chloroquine and hydroxychloroquine are useful in the treatment of cutaneous and mucosal disease.

Our approach to the management of sarcoidosis has been to commence treatment with prednisolone (1 mg/kg) in order to achieve rapid disease control. In patients with severe disease not responsive to corticosteroids, in patients whose disease relapses on dosages of prednisolone of more than 15 mg/day, or in patients who have severe steroid side-effects, an additional steroid-sparing agent is used. This is most frequently azathioprine (2–3 mg/kg/day), cyclosporin (2–5 mg/kg/day) or cyclophosphamide (2–3 mg/kg/day). We have avoided the use of methotrexate because of its propensity to cause hepatic and lung disease, which may be confused with disease progression.

**References**