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## Basic Diagnostic Approaches in Sarcoidosis

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### 1. Introduction

Sarcoidosis was first described by a British dermatologist, Jonathan Hutchison in 1869. Since then it has been seen in almost every part of the world and continues to engender considerable interest and concern amongst scientists and medical providers alike because 1) the cause is unknown, 2) it may involve any organ system in the body, 3) the course and prognosis vary from spontaneous resolution to progressive disability and death, and 4) there is no truly satisfactory treatment. Just as there are many unknowns about the illness in general, its diagnosis remains problematic despite extensive study and voluminous reporting in the scientific literature. Our objective in this chapter is to provide an overview of current knowledge on the diagnostic approach in sarcoidosis.

### 2. Definition

Sarcoidosis is a granulomatous disease of unknown etiology with protean manifestations that affects people throughout the world (1).

### 3. Diagnostic criteria

In many respects, sarcoidosis is a diagnosis of exclusion. Although it has been asserted that the method of diagnosis has been established (1), a more recent expert view is that the diagnosis is never completely secure (2). There is no single diagnostic test. It is often suspected when a chest radiograph performed for non-specific symptoms such as dyspnea or chest pain shows the characteristic findings of bilateral hilar adenopathy with or without diffuse lung infiltrates. In other cases, especially when thoracic manifestations are atypical or absent, the diagnosis remains obscure. Thus, the diagnostic approach may be straightforward, but in some situations will be complex and involve multiple diagnostic modalities. The diagnosis of sarcoidosis is based on the following criteria: 1) a compatible clinical and/or radiographic picture 2) histological evidence of non-caseating granulomas and 3) exclusion of other conditions with similar histology. An algorithm for approaching the diagnosis which reflects currently available data is shown in figure 1. The diagnostic evaluation should also evaluate the extent and severity of organ involvement, and assess disease stability and the need for treatment with corticosteroids (1).

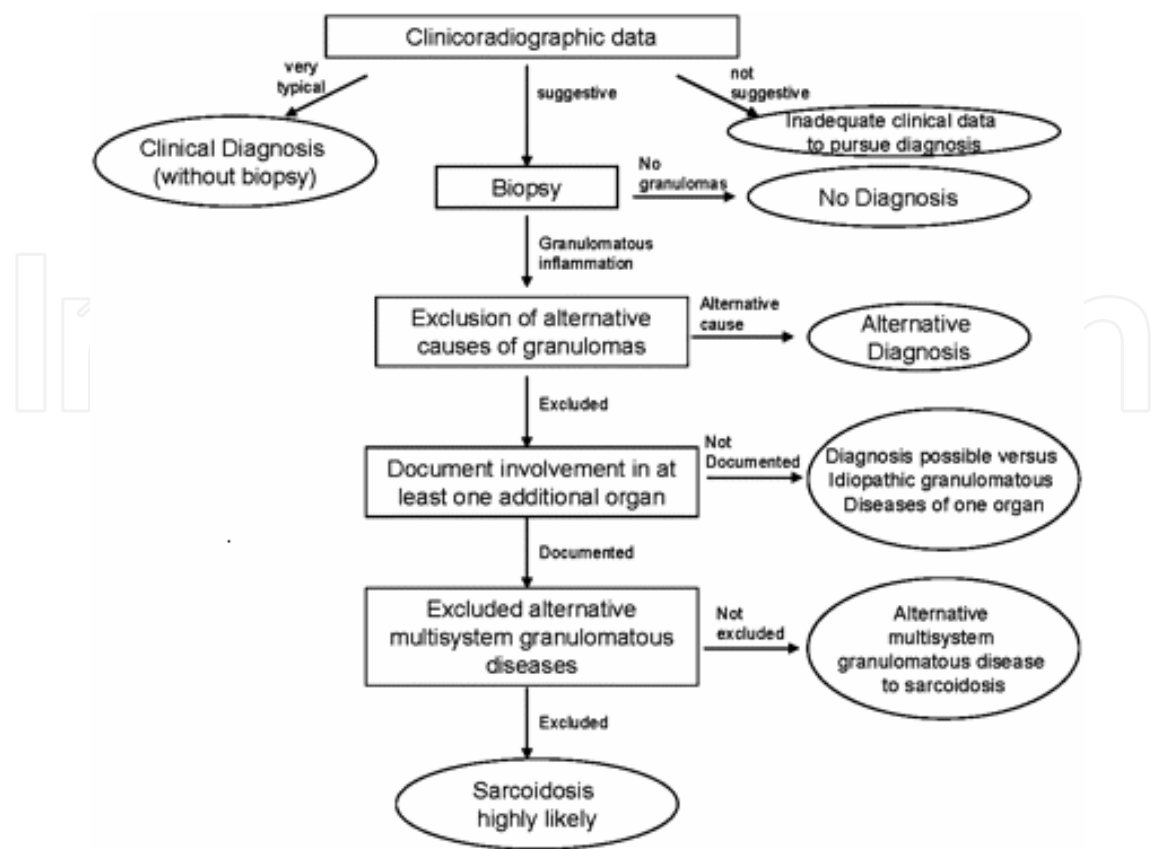


Fig. 1. An approach to the diagnosis of sarcoidosis\*

4. Initial evaluation

Key data from the medical history, physical findings, and routine laboratory and radiographic studies figure prominently in the diagnostic approach to sarcoidosis. Nonspecific constitutional manifestations such as fever, fatigue, malaise, and weight loss occur in up to one third of patients with sarcoidosis (3). Sarcoidosis can involve virtually every organ system and the review of systems can provide important diagnostic clues. Factors associated with a higher clinical likelihood of sarcoidosis include African American or Northern European descent, nonsmokers, and a family history of sarcoidosis (4-7). A detailed occupational history should include prior exposure to beryllium, risk factors for hypersensitivity pneumonitis, and exposure to tuberculosis or fungal pathogens all of which can mimic sarcoidosis (1).

The physical examination should be performed with similar attention to detail. Respiratory findings may include wheezing or rales. Frequently encountered extra-thoracic manifestations include peripheral lymphadenopathy, liver or splenic enlargement, ocular involvement, parotitis, facial nerve palsy, and a variety of cutaneous lesions including direct involvement by sarcoidosis and non-specific lesions especially erythema nodosum (8).

Initial laboratory studies should include a complete blood count and comprehensive metabolic panel with particular attention to liver function and calcium levels. A tuberculin skin test and (where appropriate) fungal skin tests and serologies should be done. A variety

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of electrocardiographic abnormalities may indicate cardiac sarcoidosis including conduction defects, atrial and ventricular extrasystoles and arrhythmias. Pulmonary function tests are crucial for quantification of pulmonary impairment, and to provide a baseline for assessment of future stability or progression. Restrictive and/or obstructive ventilatory defects and diffusion impairment are common.

Compatible radiographic imaging is one of the diagnostic criteria for sarcoidosis. The most common abnormalities on plain chest radiographs are bilateral, symmetric hilar adenopathy with or without lung infiltrates. The classification system developed by Scadding 50 years ago remains in use today (9). In stage I hilar and mediastinal lymphadenopathy alone are present. Stage II is defined by adenopathy plus pulmonary infiltrates, stage III by pulmonary infiltrates alone and stage IV includes radiographic evidence of pulmonary fibrosis (Figs. 2a-2d). More recently stage 0 has been added when the chest roentgenogram shows none of these abnormalities. The classification has prognostic value as originally described by Scadding with a 90% likelihood of resolution in 2 years with stage 1, compared to about 30% with stage 3. Although the radiologic staging does tend to correlate with physiologic impairment, its value in managing individual patients is limited (2).

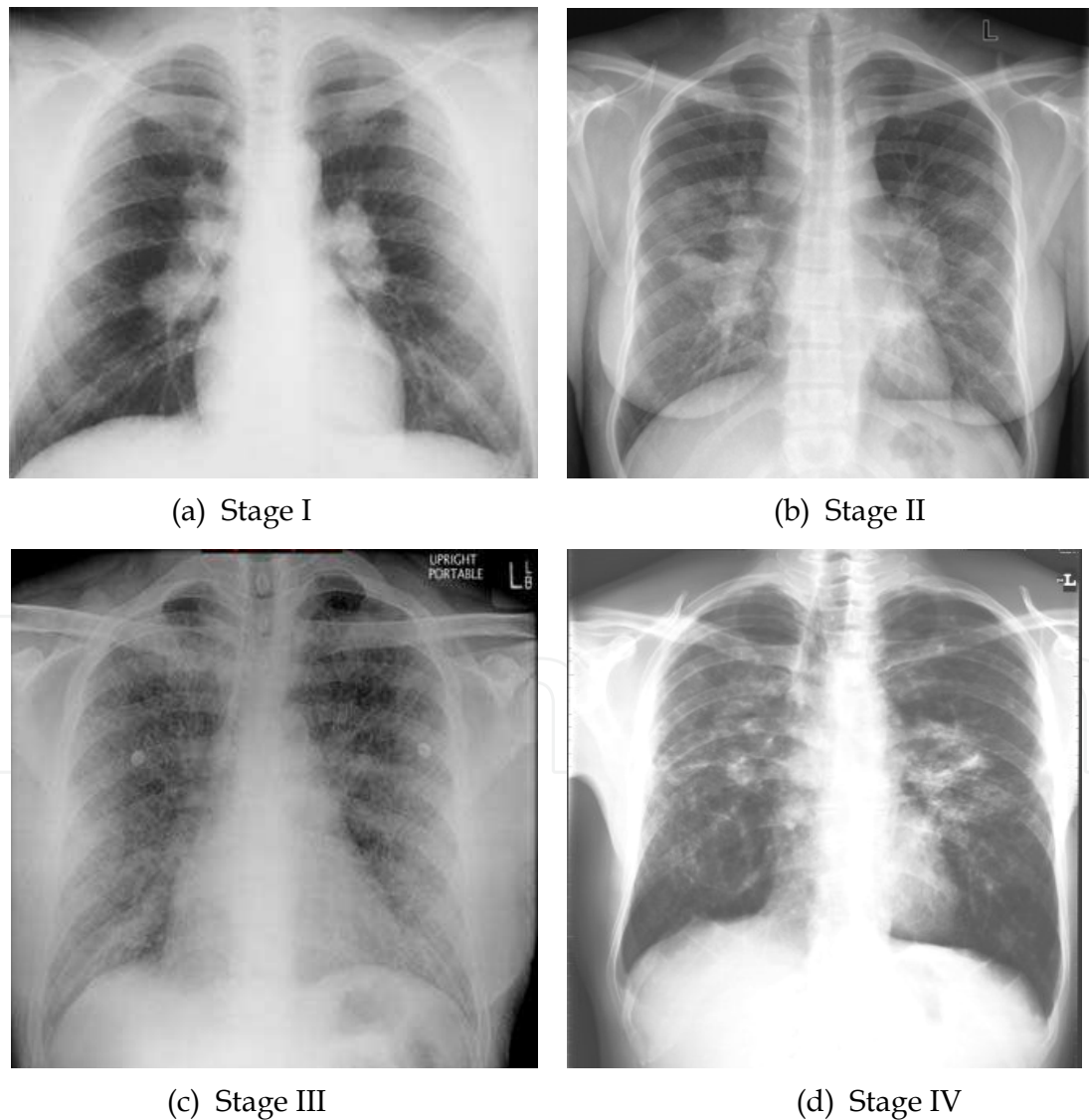


Fig. 2. Chest radiographs showing sarcoidosis stages I-IV.

Computed tomographic scans (CT scans) especially using high resolution technique (HRCT), provide much greater detail than routine chest radiographs. Common patterns in sarcoidosis include widespread pulmonary nodules, infiltrates with a bronchovascular and subpleural distribution (fig.3a), thickened intralobular septa, and as shown in figure 3b, architectural distortion, and conglomerate masses (10).

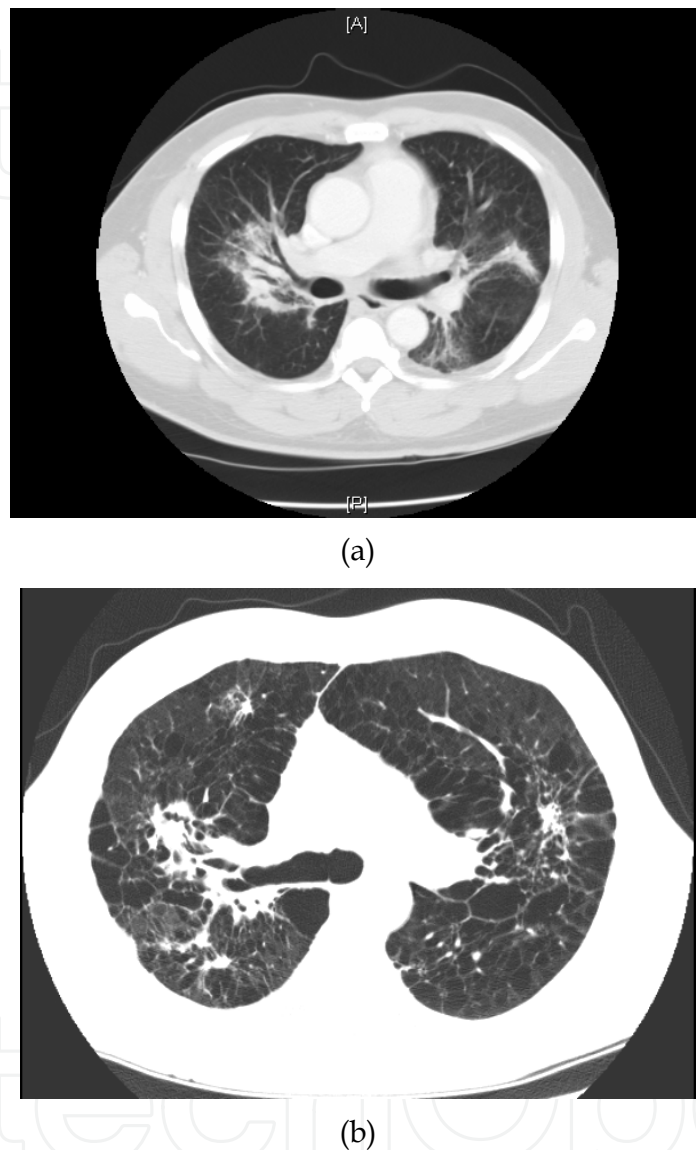


Fig. 3. (a) CT scan showing bronchovascular distribution of pulmonary infiltrates in stage III sarcoidosis.

Intrathoracic adenopathy is also more often detected on CT (11). It is unclear, however, that CT scanning adds critical diagnostic information beyond that of plain chest radiographs in the initial evaluation of most patients with suspected sarcoidosis. Whatever additional information is derived must be balanced against the added expense and radiation exposure associated with CT scans.

Gallium-67 scanning may be of value in the initial diagnostic evaluation. Parotid and lacrimal gland uptake (positive Panda sign) plus bilateral hilar and right paratracheal lymph node uptake (positive Lambda sign) strongly support the diagnosis (11) (Figs 4a,b). Like CT



scans, the additional cost and radiation exposure with gallium scanning are not warranted in most cases. Angiotensin-converting enzyme (ACE) is produced in epithelioid cells within sarcoid granulomas. Elevated levels of ACE were once felt to be diagnostic of sarcoidosis (12). More recent data indicate that ACE levels are neither sufficiently sensitive nor specific to confirm a diagnosis of sarcoidosis although they may have some value as supportive evidence for or against the diagnosis (2).

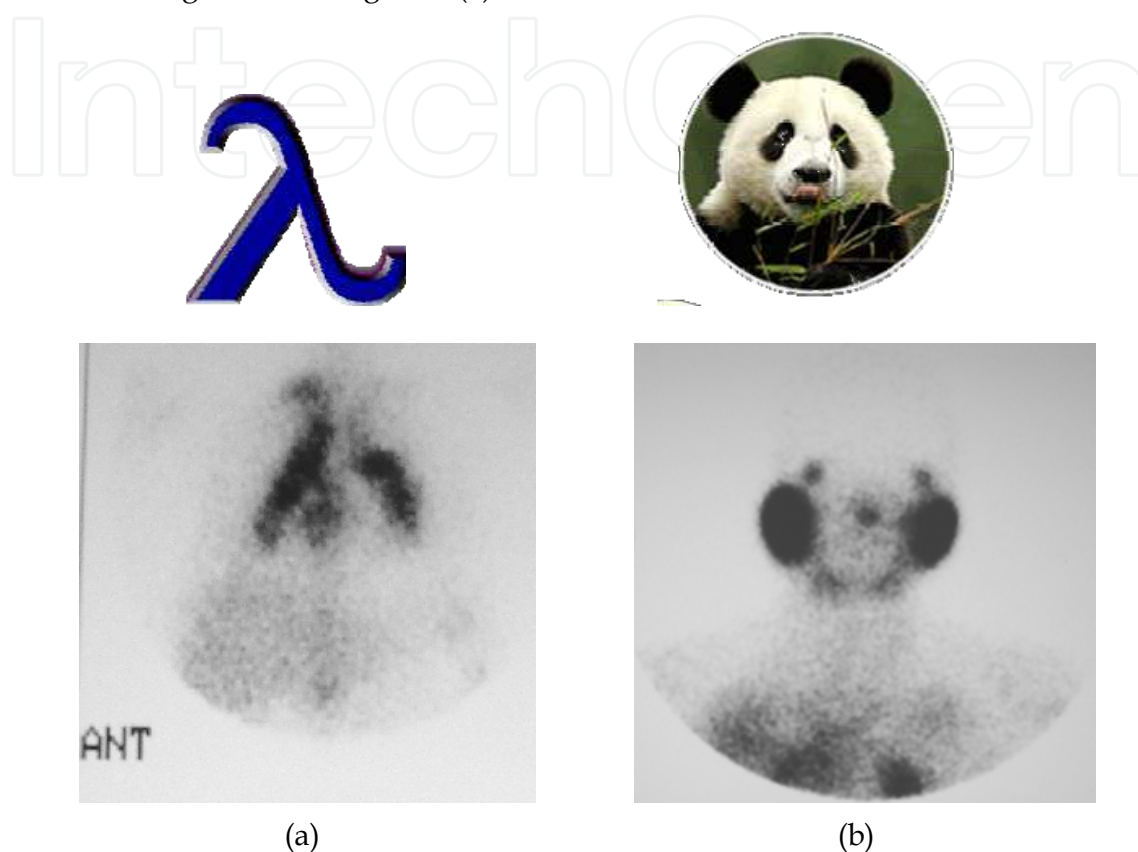


Fig. 4. (a) Gallium scan showing (a) Lambda sign; (b) Panda sign.

## 5. Diagnosis without biopsy

There are 4 circumstances where the diagnosis of sarcoidosis may be confidently made without biopsy because the combined clinical and radiographic findings are highly specific (2, 11). These situations are as follows: 1) asymptomatic patients with bilateral hilar adenopathy on chest x-ray, 2) Lofgren's syndrome which consists of bilateral hilar adenopathy, erythema nodosum, and often fever and arthritis, 3) Heerfordt syndrome which includes uveitis, parotiditis and fever, and 4) when a gallium-67 scan shows Panda and Lambda signs as previously described.

## 6. Invasive diagnostic modalities and appropriate biopsy sites

Most patients with suspected sarcoidosis require histologic confirmation for diagnosis. Since sarcoidosis is a multi-system disorder, evidence of granulomatous inflammation in at least 2 organs is required to distinguish it from granulomatous disorders of individual organs such as granulomatous hepatitis and idiopathic panuveitis (2, 11). However, biopsy confirmation

from one organ is deemed sufficient if compatible clinical, laboratory, or radiologic findings are consistent with the diagnosis in at least one additional organ and alternative diagnoses have been excluded (2, 11). Positive biopsy material from more than one organ system may be necessary when sarcoidosis presents in an atypical fashion (11).

The choice of biopsy site should be guided by what is least invasive and most likely to yield diagnostic material. Enlarged peripheral lymph nodes, skin involvement, and conjunctival nodules permit minimally invasive procedures. The Kveim test developed more than 50 years ago (13), involves a subcutaneous injection of material from a human spleen involved with sarcoidosis. A positive test is defined by the appearance of a nodular lesion at the site after 4-6 weeks which on biopsy shows non-caseating granulomas. The Kveim test has been reported to be fairly specific, but the sensitivity is low (11). It is not in general use because both sensitivity and specificity vary with the splenic material used, and it is not approved by the Food and Drug Administration in the United States (11)..

Since over 90% of patients present with intra-thoracic involvement, bronchoscopy is often the diagnostic procedure of choice. Flexible fiberoptic bronchoscopy provides multiple options for obtaining diagnostic material. Lung parenchyma can be sampled by transbronchial lung biopsy (TBLB). Granulomas may be identified via endobronchial biopsy (EBB) in the central airways. Mediastinal and hilar lymph nodes may be accessed with transbronchial needle aspiration (TBNA). Bronchoalveolar lavage (BAL) yields liquid material from one or more lung segments that can be helpful diagnostically. It also provides substrate for microbiologic studies to exclude conditions which figure strongly in the differential diagnosis, such as tuberculosis and fungal infections.

The diagnostic yield of TBLB ranges from 60% to 97% depending on the radiographic stage of the disease and the number of biopsies performed (14). In radiographic stage I where the pulmonary parenchyma appears normal on plain radiograph, the yield is approximately 50% (15, 16). Even when the lungs do not show abnormalities on HRCT, TBLB may still be diagnostic (17). The number of biopsies required to maximize diagnostic yield plateaus at 4-5 specimens (18).

Endobronchial involvement is frequent in sarcoidosis. In the presence of abnormalities of the bronchial mucosa including nodularity, hypervascularity and bronchial stenosis, EBB has been reported to be diagnostic in over 90% of cases (19). Even when the mucosa appears normal, a positive biopsy may be obtained in about 30% of cases (19, 20). Moreover, the addition of EBB to TBLB increases overall diagnostic yield (19, 20). EBB should probably be considered in all patients undergoing bronchoscopy for suspected sarcoidosis since it adds minimally in terms of risk and procedure time.

Bronchoalveolar lavage (BAL) can be of value in the diagnosis of sarcoidosis. Analysis of BAL fluid typically shows a normal or modestly increased cell count, a lymphocyte predominance in over 90% of patients, a normal percentages of neutrophils and eosinophils, and absence of foamy alveolar macrophages and plasma cells (10, 21). These findings are helpful in distinguishing sarcoidosis from several conditions with similar clinical and radiologic features, specifically, extrinsic allergic alveolitis, nonspecific interstitial pneumonia, and idiopathic pulmonary fibrosis. Examination of lymphocyte populations (CD4/CD8 ratio) may also be diagnostically helpful. Several studies have shown that a CD4/CD8 ratio of greater than 3.5 has a specificity of 93-96%, although the sensitivity is low (53-59%) (22-25). In inactive sarcoidosis, the ratio is usually normal. In patients with only

extrathoracic manifestations, BAL may still show findings typical of sarcoidosis even when thoracic imaging studies are normal (26).

Endobronchial ultrasound (EBUS) is a new approach to obtain histologic confirmation of intrathoracic sarcoidosis. Formerly, transbronchial needle aspiration (TBNA) using anatomical landmarks and fluoroscopy to guide the site of needle insertion in the airway was the standard bronchoscopic technique for sampling mediastinal lymph nodes in suspected sarcoidosis and other conditions particularly bronchogenic carcinoma. The ability to visualize lymph nodes via EBUS has resulted in diagnostic yields in sarcoidosis approaching 85% in experienced hands (27, 28). In one study, the diagnosis was confirmed in 96% of patients using EBUS compared to 73% using TBNA without EBUS despite the use of smaller gauge needles (19g for TBNA alone vs 22g with EBUS) (29). Furthermore, EBUS has the added ability to biopsy smaller nodes not easily accessible by blind TBNA or mediastinoscopy. Procedure times and amount of sedation needed tend to be modestly higher with EBUS compared to blind TBNA. The frequency of complications is low for both techniques and roughly similar (29). Combining endoscopic (esophageal) ultrasound (EUS) with EBUS has the added advantage of accessing additional lymph node stations in the mediastinum and has proven to be an invaluable tool in lung cancer staging. In the evaluation of sarcoidosis it remains unclear if the combined modality (EBUS plus EUS) results in improved diagnostic yield (29).

When less invasive modalities are inconclusive in suspected sarcoidosis, confirmation using one of several surgical options may be necessary. Mediastinoscopy remains the “gold standard” to evaluate abnormal mediastinal lymph nodes. For mediastinal lymph adenopathy of diverse etiologies, mediastinoscopy is diagnostic in 82-97% of reported cases (30). The high yield reflects the generous volume of biopsy material obtainable with this technique. However, significant morbidity ranges from 1.4-2.3% (31). Other disadvantages include higher cost compared to less invasive procedures, the need for general anesthesia, and the cosmetic effects of a neck scar. Video-assisted thoracoscopic surgery (VATS) or open thoracotomy provide the ultimate approach for biopsy of lung parenchyma and/or mediastinal and hilar lymph nodes in sarcoidosis.

## 7. Additional diagnostic modalities

Occasionally, the clinical presentation suggests the diagnosis of sarcoidosis but no readily available biopsy site is identified, or only a single organ system is involved. Under such vexing clinical scenarios additional studies may be warranted to help identify occult sites of disease for diagnostic biopsy or to help identify the presence of granulomatous inflammation in relatively inaccessible organs (ie.. heart and brain). Traditionally gallium scanning was used in this regard, however newer modalities including F-18 fluorodeoxyglucose positron emission tomography (PET) and gadolinium enhanced magnetic resonance imaging (MRI) may have improved diagnostic sensitivity (32). FDG PET scanning has been shown to be sensitive for evaluating areas of active granulomatous inflammation in sarcoidosis. When interpreting PET scans caution is appropriate as positive scans can also be seen in patients with other granulomatous diseases, infections, and neoplasms. It has recently been proposed that combining a more specific tracer L- (3-18F) - alpha - methytyrosine scan with an FDG PET scan can help differentiate neoplasm from



sarcoidosis (33). PET scanning has also been shown to have a specific pattern in cardiac sarcoidosis.

Like PET scanning, the use of MRI in suspected sarcoidosis has been shown to have value in the identification of occult disease especially cardiac and central nervous system involvement (34). Recent studies suggest that PET scanning may be more sensitive than MRI for detection of cardiac sarcoidosis. However, MRI appears to have a higher specificity (35), and unlike PET, MRI does not expose patients to ionizing radiation.

## 8. Conclusions

The diagnostic approach in sarcoidosis can be relatively straight forward, but not infrequently it is arduous and complex. The multi-system nature of the condition, its protean manifestations, and unknown causation, all contribute to its elusive diagnostic nature. The routine clinical tools and diagnostic modalities discussed in this chapter provide an approach that will usually succeed. However, a degree of skepticism and ample consideration of alternative diagnoses are warranted.

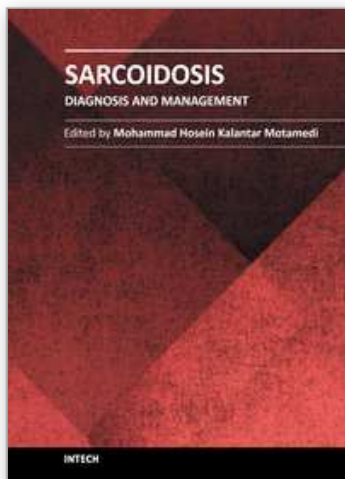
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Sarcoidosis is a type of inflammation that occurs in various locations of the body for no known reason. Normally, when foreign substances or organisms enter the body, the immune system will fight back by activating an immune response. Inflammation is a normal part of this immune response, but it should subside once the foreign antigen is gone. In sarcoidosis, the inflammation persists, and some of the immune cells form abnormal clumps of tissue called granulomas. The disease can affect any organ in the body, but it is most likely to occur in the lungs. It can also affect the skin, eyes, liver, or lymph nodes. Although the cause of sarcoidosis is not known, research suggests that it may be due to an extreme immune response or extreme sensitivity to certain substances. It also seems to have a genetic component as well, and tends to run in families. Sarcoidosis most commonly develops in people between 20 and 50 years of age. African Americans are somewhat more likely to develop sarcoidosis than Caucasians, and females are somewhat more likely to develop sarcoidosis than males. The symptoms of sarcoidosis depend on the organ involved. This book deals with the diagnosis and treatment of this mysterious disease of unknown etiology.

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