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Diagnosis of Pulmonary Sarcoidosis

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"Absolute certainty in diagnosis is unattainable, no matter how much information we gather, how many observations we make, or how many tests we perform. Our task is not to attain certainty, but rather to reduce the level of diagnostic uncertainty enough to make optimal therapeutic decision"

J.P. Kassirer, The New England Journal of Medicine, 1989

1. Introduction

1.1 Imaging

As previously described, the majority of patients with sarcoidosis are asymptomatic. The main reason patients seek medical attention is an abnormal imaging study. By far the most common situation is a chest radiography that was performed for an alternative diagnosis or as a routine procedure before anesthesia or surgery.

In recent years the increased use of computed tomography (CT) in various screening programs for malignancy (colon, lung) or in cardiology has led to an explosion of "lung abnormalities," many of which are eventually attributed to sarcoidosis. For example, 25% of solitary pulmonary nodules (SPN) on chest CT were attributable to "nonspecific granulomas" after tissue biopsy (Albert and Russell 2009).

The recent report of the National Lung Screening Trial in USA favors a CT scan program for reducing the all cause mortality attributable to lung cancer (The National Lung Screening Trial Research Team 2011). This recommendation is expected to dramatically increase the number of chest CT examinations performed for screening purposes. It is likely that many of the abnormalities found in the lung parenchyma will undergo biopsy and be diagnosed as granulomatous sarcoid-like lesions. A practical approach to their management is needed.

From a historical perspective, the suspicion of sarcoidosis is typically initiated by abnormal imaging. In fact, the pragmatic "Statement on Sarcoidosis" dedicates a subchapter to this issue in the "patient without histology" (Hunninghake et al. 1999). The authors claim that clinical and/or radiological features alone may be diagnostic for patients with stage I disease (98% reliability) or stage II (89% reliability), but less accurate for stage III (52% reliability). In a review of 100 patients with bilateral hilar lymphadenopathy, sarcoidosis was diagnosed if symptoms were limited to uveitis or erythema nodosum or in asymptomatic patients with a negative physical examination (74% of all patients). In these patients, the authors conclude that biopsy confirmation is not necessary.

1.2 The chest radiograph

The classical staging system for sarcoidosis progression was described more than 50 years ago by Scadding. In a modified version it includes:

- stage 0 : no adenopathy or infiltrate
- stage I : hilar and mediastinal adenopathy alone
- stage II : adenopathy and pulmonary infiltrates
- stage III : pulmonary infiltrates alone
- stage IV : pulmonary fibrosis (Scadding 1961)



Fig. 1. Stage I sarcoidosis on chest radiography

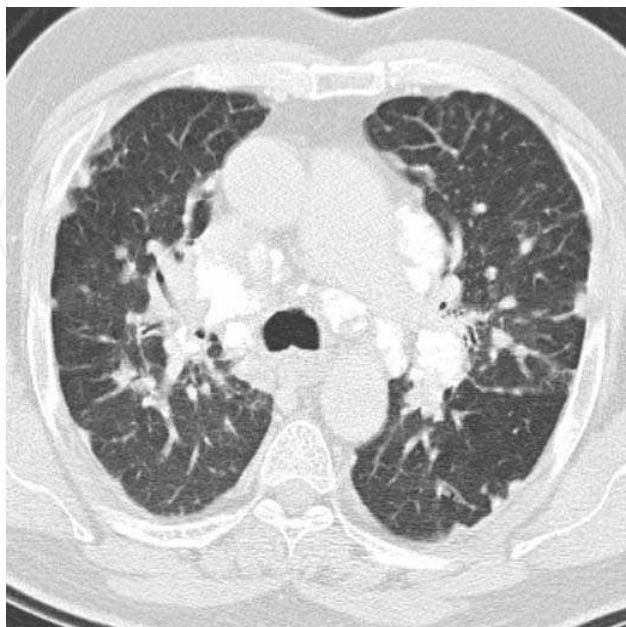


Fig. 2. Stage II parenchymal change on Chest CT



Fig. 3. Stage III sarcoidosis on chest radiography

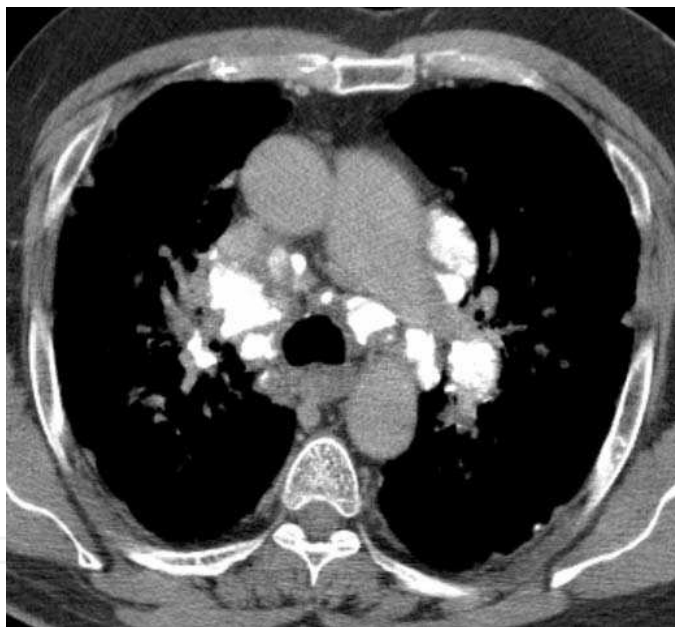


Fig. 4. Lymph node calcifications in sarcoidosis on Chest CT (contributed by Dr. Judith Rosenman, The Radiology Department, The Chaim Sheba Medical Center, Tel Aviv, Israel)

The Scadding staging system has important prognostic significance. Scadding noticed that stage I patients have more than 90% resolution of their radiographic findings within 2 years, while those with stage III disease demonstrate resolution in less than 1/3 of cases.

However, the chest radiograph does not correlate well with sarcoidosis symptoms (e.g. dyspnea) or functional parameters such as spirometry nor the six-minute walk test (Yeager et al. 2005; Judson et al. 2008; Baughman, Sparkman, and Lower 2007). Furthermore, there is poor interobserver reliability among various specialists according to a recent study of chest roentgenograms in sarcoidosis patients during a trial of infliximab (Baughman et al. 2009).

The characteristic histology of sarcoidosis is the granuloma formation. Granulomas may be seen along the lymphatics of the bronchovascular bundle, interlobular septa, major fissures and subpleural areas. These are the anatomic areas that deserve attention on regular chest X rays. The majority of patients present with stage I disease in which the differential diagnosis includes lymphoma, infectious diseases (fungal, mycobacterial) or occupational diseases (berylliosis) and support the need for biopsy confirmation.

Specific situations may preclude the need for biopsy based on radiologic and clinical findings alone. Examples include the Lofgren syndrome (bilateral hilar adenopathy, erythema nodosum, fever and arthritis), the Heerfodt syndrome (uveitis, fever and parotiditis) and the presence of isolated bilateral hilar adenopathy on the chest radiography in an asymptomatic patient. Furthermore, the Gallium 67 scan may demonstrate the typical "Panda sign" (Heerfodt syndrome) or "Lambda sign" (Lofgren syndrome) providing further support for these diagnoses and avoiding the need for histological diagnosis.

1.3 Computed Tomography (CT) scanning

With recent advances in computed tomography technology, especially the high resolution multi-slice CT scan (HRCT), the diagnostic imaging of sarcoidosis has improved. Nishino et al. describes the broad spectrum of pulmonary sarcoidosis and clues for the HRCT interpretation (Nishino et al. 2010). Disease manifestations are classified as parenchymal, airway involvement, mediastinal and hilar adenopathy and complications.

1.3.1 Parenchymal change

Nodules are the main feature of this type of interstitial lung disease. They are small (1-3 mm), peripheral in distribution and typically involve the bronchovascular bundle and interlobar septa. In our practice we use involvement of the major and minor fissures as a typical feature of pulmonary sarcoidosis. Nodules typically involve the upper lobes and lead to distortion of lung parenchyma. Less frequently, pulmonary sarcoidosis may manifest as multifocal opacities of various sizes (cm) described as "the sarcoid galaxy sign" (Nakatsu et al. 2002).

Fibrotic changes are not specific for sarcoidosis, and may represent the end stage of various interstitial lung diseases. While a honeycomb pattern is not common in fibrotic sarcoidosis (Abehsera et al. 2000), we believe fibrotic changes should discourage a decision for histological diagnosis since therapy at this stage is unlikely to affect disease evolution.

Another supportive sign of pulmonary sarcoidosis is the air trapping at end expiration on CT. In a comparative study of sarcoidosis patients with and without a history of smoking, the air-trapping sign was present in the majority of cases (Terasaki et al. 2005).

1.3.2 Airway involvement

A minority of patients with lung sarcoidosis may present with airway involvement. The small airways- lobar and subsegmental bronchi- are most commonly affected while, less frequently, disease of the large airways may manifest as tracheomalacia (Lenique et al. 1995).

1.3.3 Mediastinal and hilar lymphadenopathy

This is the main radiologic feature of sarcoidosis. Symmetric hilar adenopathy is the most typical followed by disease in the subcarina and paratracheal lymph nodes stations. Calcification and necrosis are rare features in sarcoidosis (Figure 4).

1.3.4 Complications

Hawtin et al describes sarcoidosis as the “great pretender (Hawtin et al. 2010). ” Atypical features of sarcoidosis may lead to an incorrect diagnosis and treatment. Challenging examples include:

- Aspergillosis/aspergilloma may complicate sarcoidosis
- Cavity formation may appear in large nodules due to ischaemic necrosis. Mycetoma may also complicate it (Rohatgi and Schwab 1980).
- Pleural disease including effusion occur in only 2% of cases. Chylothorax and pneumothorax were described in case reports (Huggins et al. 2006).
- Large vessel (venous/arterial) involvement is the result of external compression while necrotising angiitis on small vessels raises the possibility of other vasculitides (like Wegener’s disease)
- Lymphangitis on lung imaging raises the possibility of malignancy. The typical interlobular septal thickening is less marked in sarcoidosis than in lymphangitic carcinomatosis (Shadid and ter Maaten 2002).
- Cystic air spaces may be described in stage IV disease. They have a central distribution (in contrast to the peripheral honeycomb pattern of usual interstitial pneumonitis, UIP) and predominate in the upper lobes (Morello, Ali, and Cesani 1998).
- Diffuse mediastinal infiltration with compression of adjacent structures (Devaraj et al. 2007).
- Pulmonary veno-occlusive disease (POVD) is described in the absence of lung fibrosis (Nunes et al. 2006). Features include a high occurrence of ground glass attenuation in patients with pulmonary non-fibrotic sarcoidosis and pulmonary hypertension (sarcoid vasculopathy).
- “Vanishing lung disease” may mimic severe bullous emphysema mainly of the upper lobes (Judson 1998).

Radiologic changes provide a target for various examinations including tissue biopsy, bronchoalveolar lavage (BAL) for cytology or bacteriology investigation etc. However, the radiographic changes are not always sufficient to provide a target with significant yield. Metabolic activity at the site of the targeted lesions is essential for diagnosis and two modalities may be used for this purpose: Gallium isotope scanning or a PET examination.

1.4 Nuclear medicine

Gallium ⁶⁷ scanning is one of the oldest radionuclide imaging techniques used for sarcoidosis diagnosis. This isotope is taken up in lesions having an inflammatory or infectious cause producing an increased blood flow. Its sensitivity ranges from 60 to 90% and appears as two distinct patterns:

- the “lambda pattern”: bilateral symmetrical uptake in the parahilar and infrahilar lymph nodes and right parahilar lymph node
- the “panda pattern”: symmetrical uptake in the parotid, lacrimal and salivary glands

The presence of both patterns is regarded as highly specific for sarcoidosis (Nunes et al. 2007).

The uptake of Gallium ⁶⁷ may be noticed in other organs including the liver and spleen, but this abnormal uptake has low sensitivity and specificity. The usefulness of Gallium ⁶⁷ as a marker of disease activity is controversial (Mana 2002). Gallium ⁶⁷ scanning is a time-consuming procedure requiring up to 48-72 hours for completion and diagnosis. It is also an expensive diagnostic tool requiring isotope availability (Sulavik et al. 1990).

The [18F]-fluorodeoxyglucose-positron emission tomography (FDG-PET) is a non-invasive imaging technique widely used in oncology for the evaluation of active metabolic malignancy. Since inflammatory cells, such as neutrophils, activated macrophages and lymphocytes, also have increased FDG uptake FDG-PET is useful for both the diagnosis and/or therapeutic response in sarcoidosis.

FDG uptake in sarcoidosis was described in the early '90 s but considered neither sufficiently sensitive in uptake intensity nor specific since the pattern is also seen in lymphoma and diffuse metastatic disease (Lewis and Salama 1994). Moreover, PET-CT scans are not universally available and are expensive. The identification of potential biopsy sites is the main indication we recommend the use of either PET-CT or Gallium 67 scanning (depending on institution availability).

In a small retrospective study, Braun et al. compared the clinical utility of FDG-PET/CT and Gallium 67 scanning in biopsy-proven sarcoidosis. FDG-PET was able to provide a complete morpho-functional mapping of the inflammatory active areas and follow therapy response in patients with sarcoidosis (Braun et al. 2008). In a larger study, PET-CT helped direct the biopsy procedure and diagnose disease in difficult to reach areas such as the heart (Hollister et al. 2005). Cardiac sarcoidosis has a specific pattern and, represents, one of the main indications for PET-CT imaging in sarcoidosis. It may also be performed in patients with pacemakers. In one series, up to 40% of sarcoidosis patients had cardiac involvement based on MRI or PET-CT scanning. However, these were asymptomatic patients and the need for specific therapy was controversial (Mehta et al. 2008).

The need for differentiating malignant lesions from inflammatory/sarcoid lesions led to the use of different tracers. In a recent study from Japan, the fluorine 18 alpha methyl tyrosine tracer was used in positron emission tomography and was able to differentiate malignancy (high uptake) from sarcoidosis (negative uptake) (Kaira et al. 2007).

In conclusion, imaging is a key component in the evaluation of suspected sarcoidosis. The "classical" findings on chest radiographs and CT scans suggest the diagnosis while nuclear imaging techniques help target sites for biopsy and assess disease activity. However, results should be regarded with caution when considering therapeutic decisions because the natural history of disease is extremely variable and prognostic factors for progression of disease are lacking. Therefore, atypical radiographic presentation will usually require histological diagnosis and correlation with other diagnostic methods help decrease diagnostic uncertainty (see further in this chapter).

2. Pulmonary Function Tests (PFT)

As more than 90% of patients with sarcoidosis present with lung involvement, it is reasonable that pulmonary function tests (PFT), both static and at exercise, are affected. As mentioned in previous sections for other diagnostic tests, these PFT changes are not specific.

We use PFT for two main purposes:

- establish the disease severity
- establish the disease activity and response to therapy

A pattern of both restrictive and obstructive defects has been described. In the ACCESS study, 14-20% of the enrolled patients had a restrictive pattern and up to 13.6% had a forced vital capacity (FVC) of less than 70% on spirometry (Baughman et al. 2001). The obstructive pattern was often described in the African American population (Sharma and Johnson 1988). We have also noticed this mixed pattern in one of our patients of African Israeli origin.

The explanation of the obstructive pattern may be related to the endobronchial involvement by sarcoidosis or to airways hyperreactivity. This last phenomenon was described in up to 80% of patients with sarcoidosis, depending on the study design and patient selection (Shorr, Torrington, and Hnatiuk 2001). Symptoms of hyperreactive airways may bring the patient to medical attention but a clear connection between symptoms and PFT, especially spirometric measurements, was not established. A fixed obstructive pattern on PFT was associated with doubling the risk for mortality.

According to The Statement of Sarcoidosis, aberrations of pulmonary function tests are found in up to 20% of patients with stage I disease and up to 70% of patients with stages II, III and IV disease (Hunninghake et al. 1999).

Diffusion capacity (DLCO) measurement is characteristic for evaluation of any interstitial lung disease. As a sensitive parameter, DLCO is a marker of gas exchange impairment due to both air and vascular lung architecture disturbances. DLCO measurements are the preferred diagnostic tool to predict gas exchange disturbances during moderate exercise in patients with sarcoidosis.

In a retrospective cohort study of patients listed for lung transplantation, the single independent prognostic factor for survival was right heart ventricle hemodynamics (Arcasoy et al. 2001). This is a consequence of pulmonary hypertension and altered gas exchange as showed by other studies (Judson 1998). Therefore, gas exchange impairment as a consequence of vascular bed involvement and pulmonary hypertension may be a more sensitive parameter for sarcoidosis severity and activity. In fact, some authors suggest the DLCO measurement is the most sensitive of the pulmonary function tests in stages II-IV disease (Huang et al. 1979). Conversely, others believe that measuring diffusion capacity is not a sensitive indicator of pulmonary pathology in sarcoidosis since lung volume can be altered independently of DLCO abnormalities. It is established that gas exchange at a given degree of volume restriction differs in sarcoidosis compared with idiopathic pulmonary fibrosis (Dunn et al. 1988).

What about exercise testing? A retrospective study of 48 patients with biopsy-proven sarcoidosis suggests that changes in gas exchange with exercise may be the most sensitive physiologic measurement to assess the extent of disease in early radiographic stages of sarcoidosis (Medinger, Khouri, and Rohatgi 2001).

The 6-minute walk test is easy to perform and proved to be useful in disability assessment and prognosis in lung diseases. In a prospective study, 142 patients performed the 6-minute walk distance test and were monitored for the lowest oxygen saturation. The 6-minute walk distance was reduced in most patients but mainly in those with pulmonary hypertension. The only independent predictors of the 6-minute walk distance were the Saint George Quality of Life Questionnaire (SGRQ), the forced vital capacity (FVC) and the lowest oxygen saturation (Baughman, Sparkman, and Lower 2007).

The distance-saturation product is a new parameter defined as the product of the 6-minute walk distance and the lowest oxygen saturation during the test. This parameter was found to be well correlated with a number of factors contributing to reduced test performance. These factors are: forced expiratory volume in 1 second (FEV1), partial pressure of oxygen PAO₂, Borg dyspnea score, gender and pulmonary hypertension. This specific parameter was also associated with the degree of fibrosis documented by computed tomography (CT) and a positive response to therapy (Alhamad et al. 2010).

Dyspnea is the most common presentation in early to moderate advanced sarcoidosis. Up to half of patients have disease involvement of the skeletal muscles. Maximal respiratory

muscle force generation has been shown to be a more reliable index of functional work capacity than the standard static lung function tests (Kabitz et al. 2006).

When measuring the impairment of the inspiratory muscle strength with volitional tests (PE max, PI max), results may be misleading since these tests are highly dependent on patient motivation and cooperation. The use of non-volitional tests for this purpose may be more reliable. One of these non-volitional tests is the measurement of the twitch-mouth pressure during bilateral anterior magnetic phrenic nerve stimulation (Winterbauer and Hutchinson 1980).

So what are the most sensitive tests for evaluating sarcoidosis severity and/or disease activity? They include the static PFT based on lung volumes and diffusion capacity measurements, the exercise tests, hemodynamic evaluation and perhaps the respiratory muscle impairment serial measurements. About 30 years ago, Winterbauer and Hutchinson formulated some guidelines which we believe are still relevant in today's clinical practice:

- Pulmonary function tests data should be correlated with clinical (symptomatic) and radiological information
- There are no known PFT criteria that allow the clinician to predict the natural course of lung parenchymal sarcoidosis or response to therapy
- The best parameters to use for clinical follow up are the vital capacity (VC) and the diffusion capacity (DLCO), through sequential measurements (comparing an individual with himself through time).

The vital capacity and diffusion capacity share a common direction of change on sequential testing in 2/3 of patients with parenchymal sarcoidosis. The remaining 1/3 show a change in only one of the measured functions (Bradley et al. 2008)

As with all forms of interstitial lung disease, there has never been a formal evaluation of the diagnostic accuracy of exercise testing. In clinical practice, a normal study is useful to exclude significant interstitial lung disease in a symptomatic patient with normal rest PFT and chest radiography. The role of exercise testing in grading disease severity and prognosis is uncertain (Bradley et al. 2008).

We prefer the 6-minute walking distance test as a tool for clinical follow up and prognostic assessment along with hemodynamic evaluation of the pulmonary vascular bed (pulmonary hypertension). These measurements combined with sequential vital capacity and diffusion capacity measurements comprise a fair use of the pulmonary function tests in the diagnostic approach to sarcoidosis.

3. Biomarkers in sarcoidosis

Biomarkers are largely used in medicine for the diagnosis and follow up of a therapeutic response. Two recently published reviews (Manolio 2003; Tzouvelekis et al. 2005) describe the properties of an "ideal" serum biomarker :

- increase in the presence of disease (high sensitivity)
- normal levels in the absence of the disease (high specificity)
- add information on the risk and progression of disease
- correlate with disease activity
- correlate with disease extent/burden
- reproducible (a low coefficient of variation)
- easy/inexpensive determination

Such an ideal serum biomarker is difficult to find in most of the systemic diseases and sarcoidosis is not an exception. Sarcoidosis is a systemic inflammatory disease and so most of the biomarkers are serum markers of disease activity. They include various cytokines, enzymes, soluble cytokine receptors and various proteins.

Following the widespread use of flexible bronchoscopy and the technique of the bronchoalveolar lavage (BAL), a score of immunologic studies were performed on cell populations obtained from the respiratory epithelium. They include both bronchial and alveolar cell origin.

In two separate studies, Ziegenhagen et al. described the TNF alpha, released by the macrophages, and the serum level of sIL-2R as reliable biomarkers reflecting sarcoidosis severity and prognosis (Ziegenhagen et al. 2003).

In a well-designed retrospective study, the clinical usefulness of various serologic markers of inflammation were studied in 185 sarcoidosis patients followed in a dedicated sarcoidosis center for 4 years (Rothkrantz-Kos et al. 2003). Disease severity was assessed by ROC curves and logistic regression analyses. The disease severity was also compared to the lung function tests results. The sIL-2R had the largest area under the curve (AUC) in the untreated patients. The same parameter had the highest sensitivity, specificity, positive and negative predictive values among all the evaluated markers.

So what is the sIL-2R marker? In sarcoidosis, activated alveolar macrophages produce interleukin 1 and 6 (IL-1 and IL-6). The cytokines stimulate the production of SAA (serum amyloid A) and IL-2. The IL-2 production leads to T cell activation which express the IL-2 receptor on their surface IL-2R and release a soluble form of it in serum (s IL-2R). The s IL-2R marker was found to be increased in active disease (Muller-Quernheim 1998).

Another biomarker is derived from the lung epithelium specific proteins. The pneumoprotein KL-6 (Krebs von den Lungen) was initially described as a marker of sarcoidosis by Kobayashi et al. Increased serum levels of KL-6 indicated alveolitis activity and disease severity (Kobayashi and Kitamura 1996).

In a recent retrospective study from Japan, 43 patients with pulmonary sarcoidosis were observed. The initial serum IL-2R, lysozime and KL-6 levels reflected lymphocytic alveolitis. The initial serum KL-6 level was also associated with increased parenchymal infiltration (Miyoshi et al. 2010). This was also demonstrated by a strong correlation between the serum IL-2R and KL-6 markers levels and the bronchoalveolar lavage (BAL) fluid number of total lymphocytes and CD4.

By far the most studied and controversial serum marker for sarcoidosis is the angiotensin converting enzyme (ACE). Elevated levels were found in up to 60% of the patients with active sarcoidosis (Sharma and Alam 1995). This is an exopeptidase playing a central role in the control of blood pressure through conversion of the decapeptide angiotensin I to the octapeptide angiotensin II and through bradykinin inactivation. Most of the angiotensin I-angiotensin II conversion occurs through a single lung passage. ACE activity takes place on the luminal surface of the pulmonary endothelium but also on non-pulmonary vascular bed (Ng and Vane 1967).

In his pioneer study from 1975, J. Lieberman measured the serum ACE level in 200 patients with chronic lung disease and 200 controls (Lieberman 1975). While the serum ACE level was reduced in patients with COPD, CF, tuberculosis and lung cancer, the ACE level was significantly higher in sarcoidosis (greater than 2 standard deviation above the mean) for 15 of 17 patients with the disease. In sarcoidosis patients treated with steroids the level was normal. He concluded that an assay of serum ACE is useful for confirming sarcoidosis diagnosis and monitoring therapy.

Both ACE and angiotensin II were found in the epithelioid cells of sarcoid granuloma, but not in macrophages and monocytes (Pertschuk, Silverstein, and Friedland 1981). In a review article, Studdy and Bird analyzed the value of serum ACE (SACE) in clinical practice. As a diagnostic test for sarcoidosis, SACE demonstrated a 84% positive predictive value and 74% negative predictive value. They described SACE as a useful tool for measuring both pulmonary and extrathoracic sarcoidosis activity. They also suggested SACE as a marker of response to corticosteroid therapy since the SACE level became normal in treated patients within 4-10 weeks. However, an elevated SACE activity is not exclusive to sarcoidosis and a low SACE level does not exclude the disease (Studdy and Bird 1989).

Another large study of SACE level in 1,941 sarcoidosis patients demonstrated a positive predictive value of 90%, negative predictive value of 60%, sensitivity of 57% and specificity of 90% (Baughman, Culver, and Judson 2011).

In addition to sarcoidosis, other diseases associated with elevated SACE levels include disseminated tuberculosis, fungal infections, hyperthyroidism and Gaucher's disease (Baughman, Culver, and Judson 2011). It is believed that the serum ACE level reflects the total granulomatous load. This level may be influenced by the presence of specific or non-specific ACE inhibitors such as albumin and its fragments, fibrinolytic products, insulin including its beta chain (Klauser et al. 1979). Immunoassays of ACE concentration avoid this problem and allow the calculation of the specific activity of ACE. A radio-immune assay was developed and showed a strong correlation with serum ACE activity (Brice et al. 1995). However, another study showed that serum ACE level does not correlate with sarcoidosis severity (Pietinalho et al. 2000).

The controversy is furthered by polymorphisms of the ACE gene which lead to changes in the serum enzyme level. To elucidate the role of the insertion (I)/deletion (D) polymorphism of the ACE gene, a case control study was performed in two different patient populations: Afro-Americans and Caucasians. In Afro-Americans, the increased risk for sarcoidosis was 1.30 (95% confidence interval) for ID heterozygotes and 3.17 (95% confidence interval CI: 1,50-6,71) for DD homozygotes (Maliarik et al. 1998). In the study of a European white population, no association was found between the ACE I/D polymorphism and pulmonary disease activity, fibrosis or progression. The I/D polymorphism is not a regulatory variant in this disease (McGrath et al. 2001).

A non-invasive marker of airway inflammation, especially in patients with asthma, is the fraction of end tidal exhaled nitric oxide (FeNO). In a feasibility pilot study, FeNO was used to detect and monitor therapy response in patients with sarcoidosis (Choi et al. 2009). These exhaled NO measurements were not useful for monitoring disease progression in sarcoidosis.

An ideal biomarker for sarcoidosis does not exist yet. The main limitation is the insufficient sensitivity and specificity of the biomarker. Practically, ACE activity is still the most often used marker for disease activity despite its limitations. It is relatively cheap and easy to perform in a standard laboratory and may support the clinical and radiologic features suggestive of a sarcoidosis diagnosis. Its value as a marker for therapeutic response in those treated with corticosteroids is debatable.

4. Histology

Sarcoidosis is defined as a systemic disorder of non-necrotizing granulomatous inflammation in affected organs. Almost any organ may be involved but the lungs and intrathoracic lymph nodes are by far the most commonly affected (Saldana 1994). In addition to the careful correlation of clinical and radiologic features, the diagnosis requires

the histologic confirmation of granulomatous inflammation and the exclusion of known causes of systemic granulomatous disorders. It is not an easy task for the pathologist.

Sarcoidosis is one of modern medicine's "great mimicker's." In addition to important alternative diagnoses such as lymphoma, tuberculosis, fungal and other infections, unusual presentations include the Guillain-Barre syndrome (Shah and Lewis 2003), metastatic Crohn's disease (Emanuel and Phelps 2008), and even pulmonary embolism (Morello, Ali, and Cesani 1998). In the retrospective analysis of 30,000 surgical pathology reports, 3% revealed granulomatous lesions of which only 1/3 were considered relevant to the clinical diagnosis. Of the primary granulomatous disorders, an estimated 1/3 were attributable to infection and sarcoidosis (Woodard et al. 1982).

This section will focus on the histologic features which support the diagnosis of sarcoidosis and available methods in obtaining histologic specimens.

4.1 Granulomatous inflammation

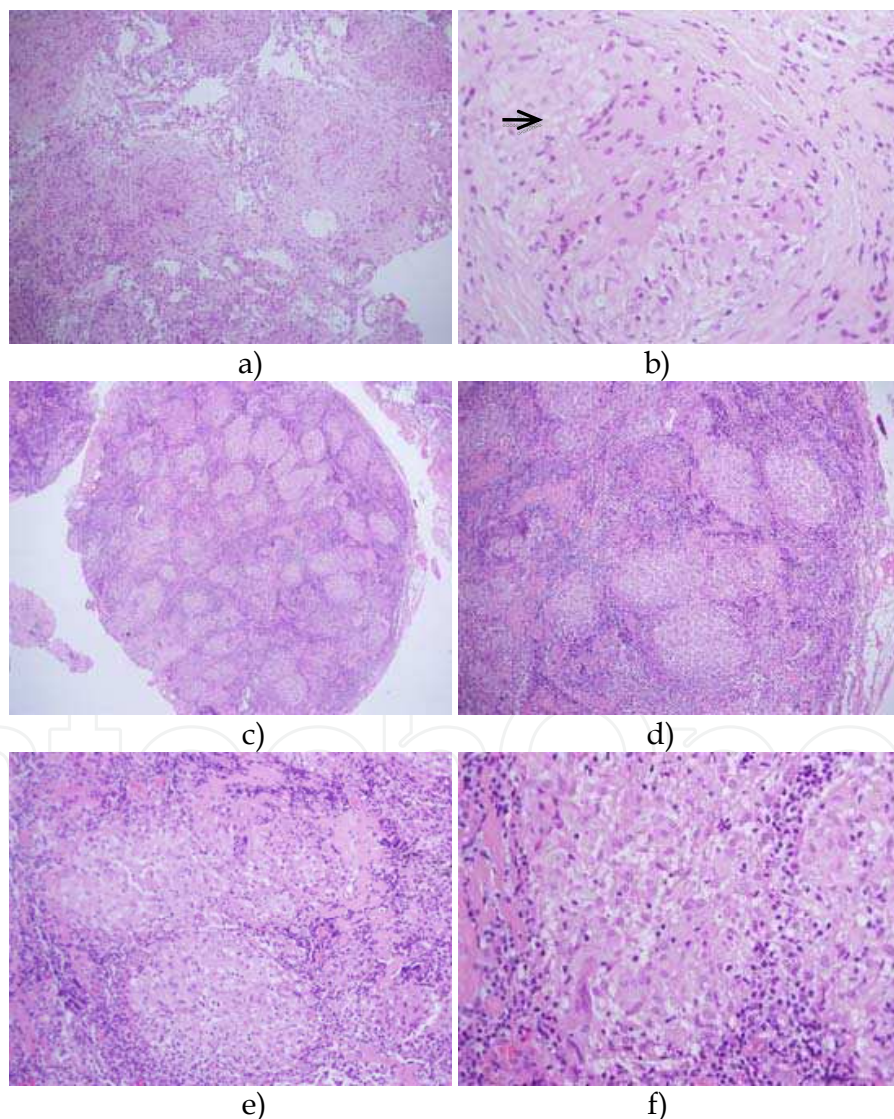


Fig. 5. Lung and lymph node biopsies at different magnification demonstrating the typical non-necrotizing granulomatous lesions of sarcoidosis (contributed by Marina Perlman, M.D., Department of Pathology, The Chaim Sheba Medical Center, Tel Aviv, Israel)

A granuloma is the compact aggregation of histiocytes (activated macrophages). They are also named “epithelioid” histiocytes because of their indistinct cell borders with elongated nuclei in contrast to typical histiocytes with well-defined borders and round or kidney bean-shaped nuclei (Mukhopadhyay and Gal 2010). The hematoxylin and eosin (H&E) preparation demonstrates the pale pink granular cytoplasm and indistinct cell boundaries which appear to merge into one another. They may fuse to form giant cells in the periphery and, less often, in the center of granulomas. These giant cells comprise a large mass of cytoplasm with many small nuclei arranged peripherally (Langerhans-type giant cell, Figure 5b) or haphazardly (foreign-type giant cell).

The two types of granulomas, foreign body granulomas and immune granulomas, are distinguished by both appearance and pathogenesis. Foreign body granulomas are incited by relatively inert foreign bodies. The foreign body is large enough to prevent phagocytosis by a single macrophage but its presence does not incite an immune response exemplified by lipioid pneumonia. Typically, foreign body granulomatosis is a reaction to material such as talc, sutures, or other fibers. The foreign object is often visualized in the center of the granuloma, especially if viewed with polarized light in which it appears retractile.

Immune granulomas, in contrast to foreign body granulomas, incite an immune response. Macrophages engulf the foreign material then process and present it to T lymphocytes. The activated T lymphocytes produce cytokines, such as IL-2 and IFN- γ , which perpetuate the immune response and transform macrophages into epithelioid cells and multinucleate giant cells. These cytokines are essential to both the formation and maintenance of granulomas.

4.2 Granuloma classification

Granulomas are classified as either necrotizing or non-necrotizing. Necrosis occurs when the trigger invokes a significant delayed hypersensitivity response or is highly toxic to the macrophage. According to Rosen (Saldana 1994), caseous necrosis refers to the cheeselike gross appearance and not to microscopic features. The terms “caseous,” “caseating” and “noncaseating” have no diagnostic relevance and may be misleading because of the association with tuberculosis. For this reason, granulomas are best reported as necrotizing, non-necrotizing, or exhibiting minimal necrosis.

4.3 Histologic features of sarcoidosis

Sarcoidosis is classically characterized by discrete, well-formed non-necrotizing epithelioid granulomas tightly uniform in their size and stage of development (Saldana 1994). Macroscopically, granulomas may coalesce to form small nodules which may be palpable as 1-2 cm non-caseating consolidations. In chronic disease, the granuloma may be surrounded by concentric, lamellated fibrous rims or even replaced by fibrous scars. Classic sarcoidosis is also supported by the absence of certain features. For example, the absence of interstitial inflammation in areas without granulomas, the absence of organizing pneumonia, and the absence of granulomas within alveoli further characterize classic sarcoidosis.

The classic granulomas in sarcoidosis are non-necrotizing but the presence of necrosis is not uncommon. When necrosis is present, however, it is usually “minute, spotty and inconspicuous” affecting the central core of a small proportion of granulomas. The necrosis seen in tuberculosis and other infectious diseases may be indistinguishable from that seen in sarcoidosis (Saldana 1994).

“Sarcoid reactions” deserve special mention. These are non-caseating granulomas which are morphologically identical to those seen in sarcoidosis yet secondary to a primary process. Such reactions have been reported in patients with lymphoma, non-small carcinoma of the lung, draining lymph nodes of germ cell neoplasm and even in remote lymph node stations (Mehrotra and Dhingra 2010). Indeed, sarcoidosis may precede malignancy in hematologic malignancies (the sarcoidosis-lymphoma syndrome), the full spectrum of solid tumors, and as a paraneoplastic syndrome for the associated cancer (Cohen and Kurzrock 2007).

Intracytoplasmic inclusions are frequently found in sarcoidosis. Schaumann bodies are calcified structures often present within the giant cells. Colorless, birefringent crystals may also be seen within the cytoplasm and often together with Schaumann bodies (Saldana 1994). They are reported in up to 88% of cases of sarcoidosis but are nonspecific findings and also seen in 62% of berylliosis, and 6% of tuberculosis cases.(Saldana 1994)

Asteroid bodies are star-like inclusions with 30 or more rays originating from the central core. Less frequent than Schaumann bodies, they are reported in 2-9% of sarcoidosis specimens (Saldana 1994). Hamazaki-Wesenberg bodies are giant intracellular and extracellular lysosomes seen in both granulomatous and nongranulomatous lymph nodes of sarcoidosis as well as other etiologies. They may be mistaken for fungi because the yellow-brown pigment may stain positive with methenamine silver and may demonstrate a yeast-like budding appearance (Ro et al. 1987; Saldana 1994)

These inclusions, while described in sarcoidosis, are found in many other granulomatous diseases such as hypersensitivity pneumonitis, berylliosis, fungal infection, talc, tuberculosis and nontuberculosis mycobacterial infection. (Mukhopadhyay and Gal 2010; Reid and Andersen 1988). The online atlas of granulomatous diseases by Yale Rosen, M.D is an excellent resource to visualize all these features (<http://granuloma.homestead.com/>).

In summary, sarcoid granulomatous lesions are compact, uniform non-necrotizing epithelioid granulomas which may exhibit a mild degree of focal necrosis and a variety of inclusion bodies. However, no morphologic feature is specific or diagnostic of sarcoidosis.

4.4 Pulmonary sarcoidosis

Although any organ may be affected, lung or intrathoracic lymph node involvement is present in more than 90 percent of patients with sarcoidosis. It is the most common noninfectious cause of lung granulomas observed by surgical pathologists (Mukhopadhyay and Gal 2010). While no finding is pathognomonic for pulmonary sarcoidosis, classic features may support the diagnosis while their absence encourages the search for an alternative diagnosis. The varied presentations of pulmonary disease will be described.

Granulomas are typically found bilaterally in the upper two thirds of the lungs and in areas rich in lymphatics (the peribronchial, perivascular and septal regions). This “lymphatic” distribution explains the radiographic appearance which may “mimic” primary neoplasm or lymphangitic spread. It also explains the effectiveness of trans-bronchial biopsies in demonstrating sarcoid granulomas. In addition, the alveoli, bronchi, pulmonary blood vessels, and the pleura may all be involved.

Alveolitis is the earliest pulmonary lesion and is characterized by a lymphocyte-predominant interstitial pneumonitis. A high proportion of CD-4 positive cells are found in bronchoalveolar lavage (BAL) (Baughman, Lower, and du Bois 2003). In one study, a lymphocyte CD4/CD8 ratio greater than 3.5 showed 53% sensitivity but 94% specificity for the diagnosis of sarcoidosis (Costabel 1997). These CD4+ T cells, activated by a complex

network of cytokines and chemokines, infiltrate at sites of disease and may play a role in the sarcoid granuloma formation. In a recent study of sarcoid patients with and without intense alveolitis, the percentage of a CD4⁺ effector T cell was much higher in patients with active disease as compared with inactive sarcoidosis (Facco et al. 2011).

The bronchi may be affected by four different mechanism: 1) extrinsic compression by enlarged lymph nodes, 2) granulomatous infiltration in the bronchial mucosa, submucosa and peribronchial tissue, 3) endobronchial mass lesion and 4) fibrotic scarring causing narrowing and distortion of bronchi. The entire spectrum of the airway may be involved from supraglottic structures and larynx to central and distal airways.

The supraglottic airway including the nasal passages, oropharynx, supraglottic structures and larynx are affected in approximately 6% of sarcoid patients (Baughman et al. 2001). Nasal ulceration may cause anosmia while infiltrative nodular sarcoidosis of supraglottic structures may cause stridor or cough. Isolated laryngeal involvement may be misdiagnosed as asthma (Bower et al. 1980). In the larynx, compression of the left pharyngeal nerve by enlarged lymph nodes may cause vocal cord paralysis (Jaffe, Bogomolski-Yahalom, and Kramer 1994).

Involvement of the trachea and main bronchi infrequently cause obstructive symptoms. In a retrospective analysis of 2,500 sarcoidosis patients, only 18 patients were identified with significant (defined as >50% of the lumen) endoluminal stenosis of proximal bronchi (ESPB). Despite the small number of patients, it is important to note that the group with early diagnosis and treatment (<3 months from onset of symptoms) were associated with good prognosis in contrast to patients with delayed diagnosis and treatment (>3 months from onset of symptoms)(Chambellan et al. 2005).

In the bronchi, granulomatous lesions most frequently involve the distal bronchial tree and develop along the bronchovascular bundle or near the airway with predominance for the upper and mid-lung regions. Various airway abnormalities develop and will be described.

The most common endobronchial abnormality is mucosal edema, erythema or granularity but normal-appearing mucosa does not exclude disease. Classic endobronchial sarcoidosis is characterized by mucosal islands of nodules which appear a waxy yellow or dull gray. Coalescence of these nodules is responsible for the cobblestone appearance while endoluminal occlusion may mimic an obstructing mass.

Bronchiolitis may occur early in disease without parenchymal involvement. However, airway distortion and bronchiectasis is more prevalent with progression of parenchymal disease. In advanced fibrotic disease, cystic lesions and cavitary disease predispose to *Aspergillus* infection. The development of an aspergilloma may cause hemoptysis and massive, life-threatening hemoptysis may occur (Stevens et al. 2000)

Airway Hyperactivity in patients with sarcoidosis is well described. In the prospective evaluation of 42 patients with newly diagnosed sarcoidosis and pulmonary symptoms, 20% demonstrated AHR by methacholine challenge. Endobronchial biopsies demonstrated noncrotizing granulomas in 100% of these AHR-positive patients but only 45.5% of patients without AHR (Shorr, Torrington, and Hnatiuk 2001).

In the pulmonary vascular system, sarcoid lesions involve the veins much more frequently than the arteries and damage may range from destructive change in the media to stenosis or complete obliteration of the lumen (Saldana 1994). Although vascular involvement is common, the overall prevalence of pulmonary hypertension is low (5%). Although most affected patients have stage IV radiographic disease, two distinct phenotypes of sarcoidosis and pulmonary hypertension (PH) may exist depending on the presence or absence of pulmonary fibrosis.

In the study of 22 patients with sarcoidosis and pulmonary hypertension, 1/3 developed pulmonary hypertension in the absence of pulmonary fibrosis and no other known cause of secondary pulmonary hypertension (Nunes et al. 2006). These patients had near normal or mild restrictive spirometry but severely reduced DLCO. These findings suggest that PH in these patients may be explained by a specific vasculopathy independent of fibrotic destruction of the vascular bed. According to the authors, the presence of septal lines and ground glass opacities on HRCT suggest the possibility of pulmonary vascular occlusive disease from granulomatous involvement of the venous walls. These radiographic features are shared by pulmonary histiocytosis X, a granulomatous disease with intrinsic venopathy. Honeycombing is the end stage of many interstitial diseases including sarcoidosis. In contrast to UIP, honeycombing in sarcoidosis is found predominantly in the upper lung zones. Bronchiectasis and emphysematous change may be seen but few granulomas are evident at this late stage. An important complication of the cystic parenchymal disease is the development of aspergillomas, which may cause life-threatening hemoptysis (Rumbak et al. 1996; Wollschlager and Khan 1984).

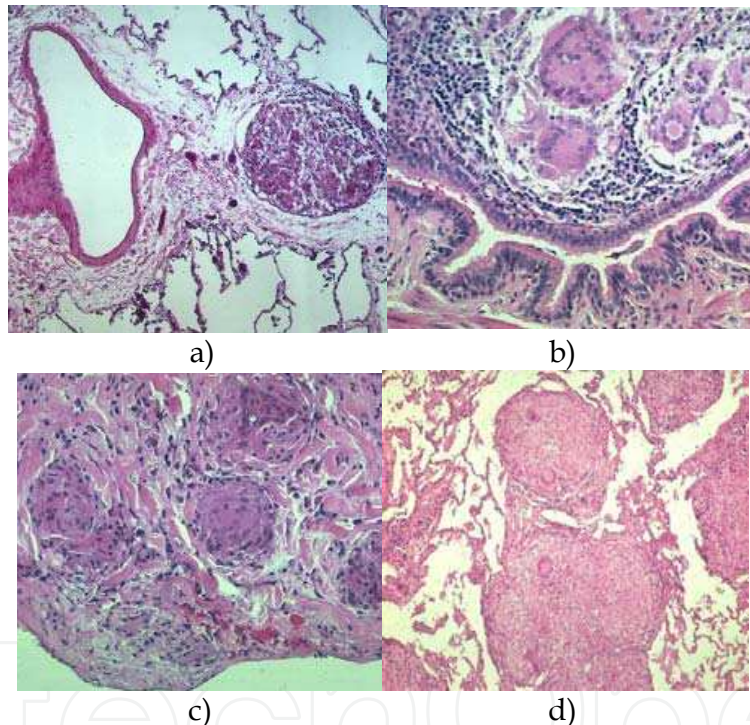


Fig. 6. Pulmonary sarcoidosis affecting a) the lymphatics b) the bronchiole c) the visceral pleura and d) coalescing to form nodular disease. (Contributed by Yale Rosen, M.D.)

4.5 The diagnostic approach

Special clinical situations may preclude the need for tissue biopsy. These include the Lofgren and Heerfodt syndrome as well as isolated bilateral hilar lymphadenopathy in asymptomatic patients. As mentioned, the “panda” sign (Heerfodt syndrome) and the “lambda” sign (Lofgren syndrome) on Gallium-67 scanning further support the diagnosis of sarcoidosis and avoid the need for tissue confirmation. Excluding these unique clinical syndromes, histologic confirmation is required.

In general, the easiest accessible site is used for tissue biopsy which may include the skin, an enlarged superficial lymph node or lacrimal gland. Non-necrotizing granulomas on a liver

or bone marrow biopsy are non-specific and support the diagnosis of sarcoidosis only when competing diagnoses such as infection, malignancy or drug reaction have been excluded.

Pulmonary involvement is seen in 90% of patients with sarcoidosis in which intrathoracic lymphadenopathy is the most common finding (Hughes and Hill 2009). In the absence of an easily accessible biopsy site, fibroscopic bronchoscopy is preferred for its relative safety and high yield. The various techniques include bronchoscopic alveolar lavage (BAL), transbronchial lung biopsy (TBLB), transbronchial needle aspiration (TBNA), and endobronchial ultrasound (EBUS)-guided TBNA and will be discussed below.

In the lung, 75% of granulomas are distributed near or within the connective tissue sheath of bronchioles and subpleural spaces, "following the lymphatics" as authors describe (Mukhopadhyay and Gal 2010). For this reason, the 1999 Statement on Sarcoidosis recommends transbronchial biopsy (TBB) as the procedure of choice in most cases. Diagnostic yield ranges from 40 to 90% depending on operator experience, the presence of pulmonary infiltrates and if at least four biopsies are performed.

Endobronchial biopsy may detect noncaseating granulomas in 40-60% of cases even in the absence of endobronchial nodules or cobblestone appearance (Bjermer et al. 1991). Bronchial washing is recommended for microbiologic evaluation while bronchoalveolar lavage (BAL) may provide the study of lymphocyte subpopulations. In one study, a CD4/CD8 ratio >3.5 supports the diagnosis with 94% specificity and 53% sensitivity (Costabel 1997; Bjermer et al. 1991). However, its utility is unclear since some report a low yield of 47% (Garwood et al. 2007) while authorities report overlap with other etiologies such as infection, malignancy, and other inflammatory disorders (Fishman 2008).

When traditional bronchoscopic procedures such as EBB and TBB are nondiagnostic, further investigation has traditionally included mediastinoscopy for patients with mediastinal adenopathy and video-assisted thoracoscopic surgical lung biopsy (VATS) or open lung biopsy for patients with pulmonary infiltrates. However, advances in conventional and endobronchial ultrasound (EBUS)-assisted transbronchial needle aspiration (TBNA) may now avoid the need for surgical biopsy in most patients. Comparison of these techniques will be discussed.

The potential of EBUS-TBNA was demonstrated in a experienced, tertiary care center (Garwood et al. 2007). Fifty consecutive patients with suspected sarcoidosis underwent EBUS-TBNA with rapid on-site cytologic evaluation (ROSE). Results demonstrate safety (no major complications) and efficacy with 85% diagnostic yield. Lymph node size was not limited to >1cm and included nine nodes <1cm with 89% successful aspiration. Such results are impressive and comparable to studies of combined modalities (conventional TBNA and TBLB) but without the increased risk of pneumothorax and bleeding. However, these results are limited to experienced tertiary-care centers with the availability of ROSE.

A randomized controlled trial compared conventional TBNA with EBUS-assisted TBNA in patients with clinically suspected Stage I and Stage II sarcoidosis (Baughman et al. 2001). ROSE was not provided and lymph node size was limited to >1cm (short axis on CT scan). The EBUS-assisted TBNA procedure increased the diagnostic yield by an absolute 30% ($p<0.05$). It was 10.2 minutes longer and more patients (26.9%) received propofol for sedation. Complications were limited to moderate bleeding in two conventional TBNA attempts. Two observations deserve mention. First, the increased diagnostic yield was limited to patients with Stage 1 disease. Second, only 24% of patients in the follow-up period received specific treatment for sarcoidosis. These findings question the need to seek tissue confirmation in all patients (to be discussed further).

A large prospective, "implementation" study was designed to assess the yield of EBUS-assisted TBNA only after routine bronchoscopic procedures (EBB, TBB and conventional

TBNA) were nondiagnostic (Tournoy et al. 2010). ROSE was not available. Bronchial washing was routinely performed for microbiologic evaluation. A definitive diagnosis was obtained in 59% by routine bronchoscopy (72% TBB, 26% EBB, 14% TBNA) and 77% by EBUS-TBNA following nondiagnostic routine bronchoscopy. In other words, EBUS-TBNA following negative flexible bronchoscopy avoided a surgical procedure in 47 out of 80 patients. Overall, this implementation strategy provided a definitive diagnosis in 92% of patients. Minor complications included minor bleeding, intolerance to the procedure and one pneumothorax.

Despite the advancement in these techniques, the decision to pursue tissue diagnosis must be carefully considered especially when the diagnosis of sarcoidosis will not initiate treatment. For example, in asymptomatic patients with isolated bilateral hilar lymphadenopathy (Stage I disease), the main alternative diagnoses include lymphoma, malignancy, tuberculosis and fungal infections.

The likelihood of these alternative diagnoses may be narrowed. The probability of fungal infections is increased only when travel exposure and geographic location are suggestive. Second, the presentation of tuberculosis as bilateral hilar lymphadenopathy is rare (<1%) and systemic symptoms are invariably present. Likewise, the presentation of lymphoma is rarely asymptomatic nor limited to hilar lymphadenopathy. In fact, the *number needed to diagnosis* Hodgkin's and Non-Hodgkin's lymphoma in such patients with asymptomatic, isolated hilar lymphadenopathy is estimated at 1 in 3,600 and 1 in 33,000, respectively (Reich et al. 1998). For those who underwent mediastinoscopy, 18 patients would experience major morbidity and 36 require hospitalization.

4.6 Summary

Sarcoidosis is a disorder of unknown origin and definitive diagnosis is never certain. Typical cases of Lofgren's and Heerfodt syndrome do not require histologic confirmation. Furthermore, the risk/benefit ratio of histologic confirmation should be carefully considered when the likelihood of an alternative diagnosis is low. When histologic confirmation is desired, routine bronchoscopic procedures followed by EBUS or EUS-assisted TBNA, when needed, is a relatively safe and effective strategy applicable in most institutions.

5. Conclusion

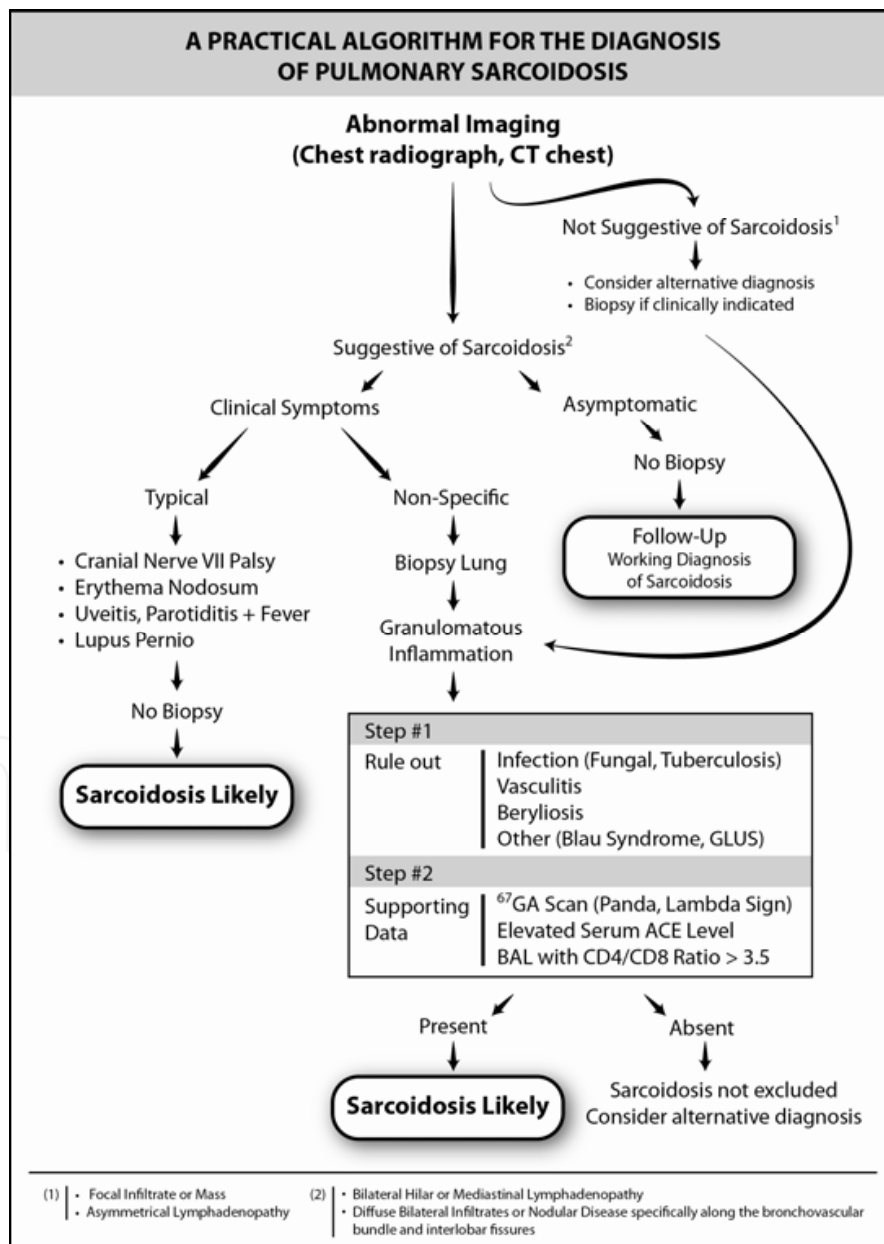
Sarcoidosis is defined as a systemic (multiorgan) granulomatous disease of unknown cause. The diagnosis is traditionally established by (1) compatible clinical and radiographic features, (2) histologic confirmation of granulomatous inflammation with evidence of systemic (multiorgan) disease and (3) the exclusion of systemic granulomatous diseases of known cause. Although histologic evidence is needed from only a single site, clinical involvement of more than one system helps exclude local granulomatous reactions to foreign bodies, tumor or infections.

In a consensus opinion of the members of the Steering Committee of the ACCESS study, a subjective instrument for determining organ involvement in sarcoidosis was proposed (Judson et al. 1999). Criteria for organ involvement in patients with biopsy confirmed sarcoidosis were described for commonly involved sites (lung, skin, eyes, liver) and those less affected (nervous system, kidney, heart, bone marrow, spleen, salivary glands, ear-nose-throat area, non thoracic lymph nodes, muscle). Although not validated in large scale prospective studies, this instrument helps define the systemic nature of disease without the necessity to histologically confirm the presence of non-necrotizing granulomatous inflammation outside the lungs.

The clinician and the pathologist must work together. The pathologist's dilemma is the differentiation of sarcoidosis from an alternative cause of granulomatous inflammation.

While infection (both fungal and mycobacterial) may be easier to diagnose today with molecular-based techniques, other illnesses such as sarcoid-like related granulomatous disease, vasculitis, granulomatous lesions of unknown significance (GLUS) or the Blau syndrome may be difficult to differentiate.

The clinician must diligently search for the clinical syndromes described that may provide a diagnosis without the need for histologic confirmation. In addition, the clinician must consider both the likelihood of an alternative diagnosis and the indications for treatment prior to recommending invasive procedures for histologic confirmation. Finally, our goal is to limit the degree of uncertainty to the best of our ability since the etiology of sarcoidosis is still unknown. This requires a careful, step-wise approach. We propose a practical algorithm based on the data provided and our experience that most patients will be referred to the pulmonologist because of abnormal findings on chest imaging.



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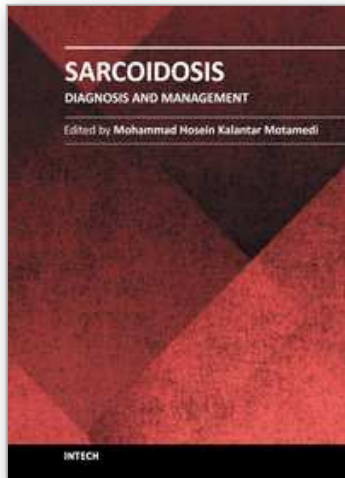
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Sarcoidosis is a type of inflammation that occurs in various locations of the body for no known reason. Normally, when foreign substances or organisms enter the body, the immune system will fight back by activating an immune response. Inflammation 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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