Sarcoidosis

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Educational Objectives:
1. Review the diagnosis of sarcoidosis for each organ system.
2. Understand imaging characteristics that can help define activity and organ involvement
3. Review the approach to treatment based on organ involvement

Ms. Hernandez is a 60-year-old female with a history of hypertension who was well until a year ago when she began to develop episodes of recurrent bronchitis. She continues to have a cough and mild shortness of breath. A chest x-ray (see below) and a chest CT was consistent with bilateral hilar and mediastinal adenopathy and small nodules in a lymphatic distribution. She has occasional fever and night sweats but no chills. She has some arthralgias in her knees and hips. She has developed a red, plaque like lesion on her chest and has had recurrent kidney stones for the last two years. She denied any palpitations, chest pain, nausea, vomiting or diarrhea. She was alert and cooperative and denied any numbness or weakness. Her PFTs are notable for moderately severe mixed obstruction and restriction (FEV1 58%). Her 6MWT was normal without evidence of ambulatory hypoxia. Her review of systems is negative. She is a never smoker and has no significant family history. Her physical exam is unremarkable other than the noted skin lesion on chest.
**Question 1: How would you approach the diagnosis in this patient? What are the clinical manifestations of sarcoidosis? What are the stages of sarcoidosis?**

Ms. Hernandez’s symptoms are consistent with a diagnosis of sarcoidosis. Clinical symptoms of sarcoidosis typically include cough (usually non-productive), dyspnea and chest discomfort. Systemic symptoms including fevers, night sweats, weight loss, depression, and myalgias may also be present. Although familial sarcoidosis can run in families, most patients have a negative family history. PFT findings can range from normal, obstructive, restrictive or mixed pictures. About 65% of patients will have airflow limitation at presentation with the most common finding being restriction although concurrent obstruction is seen in at least 50% of patients (Baughman RP, et al AJRCCM 2001).

In this case a skin biopsy might be the easiest way to document a granulomatous process. Other non-pulmonary sites to consider for biopsy include peripheral lymph nodes, lacrimal glands and conjunctiva. It is recommended to first biopsy a peripheral organ, if feasible. If the skin biopsy is negative, and there is evidence of disease in a visceral organ, like in this case, then an EBUS bronchoscopy would be performed to document granulomatous inflammation. Tissue diagnosis with pathology consistent with noncaseating granulomas is necessary to make a diagnosis in all cases with the exception of patients presenting with Lofgren’s syndrome (characterized by bilateral hilar lymphadenopathy accompanied by erythema nodosum, migratory polyarthralgias and fever), Lupus Pernio (chronic raised and indurated lesion of the skin over nose, often purplish in color; see figure 2), or Heerfordt’s syndrome (facial nerve palsy, parotid gland enlargement, anterior uveitis, and low grade fever). For patients presenting with asymptomatic, bilateral hilar lymphadenopathy, the ATS guidelines make no recommendations for or against obtaining a lymph node sample. If lymph node sampling is not obtained, close clinical follow-up is a reasonable alternative approach (Crouser et al, AJRCCM 2020). Other causes of granulomatous inflammation need to be ruled out (Tuberculosis, atypical Mycobacteria, Histoplasma, parasitic infections, ANCA Associated Vasculitis, Hypersensitivity Pneumonitis etc). Sarcoidosis is a diagnosis of exclusion based on a pattern of clinical, imaging and pathological findings (Table 1). For patients without apparent lung involvement, PET CT can be useful to identify potential targets for biopsy (liver, spleen). FDG PET and MRI with gadolinium can detect cardiac and neurologic involvement. Of note, cardiac and neurosarcoid can occur without any apparent disease activity elsewhere in the body. However, clinical sarcoidosis is manifested as intrathoracic lymph node enlargement, pulmonary involvement, skin or ocular changes in more than 90% of patients (Iannuzzi MC, et al. NEJM 2007).

![Figure 1: Lupus Pernio. Borrowed from https://dermnetnz.org/topics/lupus-pernio/](https://dermnetnz.org/topics/lupus-pernio/)
Sarcoidosis is defined as a granulomatous disease of unknown etiology that involves multiple organs. Her CXR demonstrating hilar adenopathy with enlargement of the R paratracheal, R hilar and left hilar nodes (Garland triad/“1-2-3 sign”) is a characteristic finding of sarcoidosis (seen above). Classic CT findings may include lymphadenopathy, nodularity, septal thickening, air trapping and, in severe cases, fibrosis (Davies, et al Clinical Radiology 2000). Her CT findings are also consistent with this diagnosis (Stage I disease, see Figure 1 below). Atypical findings on HRCT include large nodules, asymmetric disease, ground glass opacities, pleural effusions, and cavitation. The radiographic findings are typically organized into stages which reflect an anatomic guide of lung involvement rather than disease activity (Miller BH et al, Radiographics 1995).

<table>
<thead>
<tr>
<th>Radiographic Findings</th>
<th>Frequency at Presentation</th>
<th>Spontaneous Resolution</th>
</tr>
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<tbody>
<tr>
<td><strong>Stage 0</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal chest radiograph</td>
<td>5-15%</td>
<td></td>
</tr>
<tr>
<td><strong>Stage I</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hilar or mediastinal nodal enlargement only</td>
<td>25-65%</td>
<td>60-90%</td>
</tr>
<tr>
<td><strong>Stage II</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nodal enlargement and parenchymal disease (often upper lung zone predominant reticular opacities)</td>
<td>20-40%</td>
<td>40-70%</td>
</tr>
<tr>
<td><strong>Stage III</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parenchymal disease only</td>
<td>10-15%</td>
<td>10-20%</td>
</tr>
<tr>
<td><strong>Stage IV</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary fibrosis; reticular opacities with evidence of volume loss; +/- traction bronchiectasis; +/- calcification, cavitation or cyst formation</td>
<td>5%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Table 2. Overview of sarcoidosis stages based on imaging characteristics
Question 2: What additional studies should you consider at the time of the EBUS bronchoscopy?

- Trans-tracheal needle aspiration of mediastinal lymph nodes for culture, immunophenotyping and cytology. EBUS has a diagnostic yield of approximately 80-90% in patients with mediastinal adenopathy and clinical suspicion for sarcoidosis.

- BAL for culture, cell count, differential and CD4/CD8 ratio. These tests are adjunctive measures to support a diagnosis of sarcoidosis. An elevated CD4:CD8 ratio is supportive of the diagnosis. However, a finding of lymphocytosis on BAL is neither sensitive nor specific. The triad of CD4:CD8 ratio greater than 4:1, lymphocyte percentage greater than 16% and a transbronchial biopsy demonstrating non-caseating granulomas is the most specific test for sarcoidosis with a positive predictive value of 100%. A BAL fluid with more than 2% neutrophils or 1% eosinophils suggests that sarcoidosis is unlikely to be the diagnosis (Winterbauer RH, et al. Chest 1993; Drent et al. Semin Respir Crit Care Med 2007).

<table>
<thead>
<tr>
<th>Technique</th>
<th>Diagnostic Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>EBB (Endobronchial biopsy)</td>
<td></td>
</tr>
<tr>
<td>With Macroscopic abnormality</td>
<td>20-61%</td>
</tr>
<tr>
<td>Without macroscopic abnormality</td>
<td>54-91%</td>
</tr>
<tr>
<td>TBLB (Transbronchial biopsy)</td>
<td></td>
</tr>
<tr>
<td>Stage I</td>
<td>37-90%</td>
</tr>
<tr>
<td>Stage II</td>
<td>66%</td>
</tr>
<tr>
<td>Stage III</td>
<td>80%</td>
</tr>
<tr>
<td>Stage III</td>
<td>83%</td>
</tr>
<tr>
<td>cTBNA (conventional TBNA)</td>
<td>6-90%</td>
</tr>
<tr>
<td>EBUS -TBN A</td>
<td>80-94%</td>
</tr>
<tr>
<td>EUS-FNA</td>
<td>77-94%</td>
</tr>
<tr>
<td>EUS—B-FNA (transesophageal ultrasound-guided needle aspiration with the use of an echo bronchoscope)</td>
<td>86%</td>
</tr>
<tr>
<td>TBLC (Tranbronchial Cryobiopsy)</td>
<td>66.7%</td>
</tr>
<tr>
<td>TBLB+EBB</td>
<td>33.3-81.4%</td>
</tr>
<tr>
<td>EBUS TBA NA +TBLB + EBB</td>
<td>89-100%</td>
</tr>
<tr>
<td>cTBNA + TBLB + EBB</td>
<td>85.5-92.9%</td>
</tr>
<tr>
<td>TBLC+EBUS-TBNA</td>
<td>100%</td>
</tr>
</tbody>
</table>

Table 3. Diagnostic yield of different types of biopsies for making a diagnosis of sarcoidosis for sarcoidosis. Adapted from J. Clin. Med. 2019, 8, 1327; doi:10.3390/jcm8091327
**Question 3:** What studies should be done to work up the history of kidney stones?

Given concern for sarcoidosis and kidney stones, she should be assessed for hypercalcemia. Blood work including 1,25 vitamin D, parathyroid hormone levels, calcium, urinary calcium, BUN, creatinine should be performed. A biopsy of her skin is sent but was negative. Ms. Hernandez undergoes EBUS-TBNA and pathology shows noncaseating granulomas. BAL fluid is sent for cell count and shows a lymphocyte predominance (45%) with absence of neutrophils or eosinophils. The CD4:CD8 ratio is 4.2. A diagnosis of sarcoidosis is made.

**Question 4:** What other studies, examination should be done to rule out other organ involvement in sarcoidosis? What studies should she have performed to monitor her pulmonary disease?

![Diagram](image)

**Figure 2.** Proposed diagnostic algorithm for obtaining tissue to make a diagnosis of sarcoidosis based on intrathoracic tissue sampling. Adapted from J. Clin. Med. 2019, 8, 1327; doi:10.3390/jcm8091327

**Figure 3.** Clinical evaluation in sarcoidosis. Borrowed from Iannuzzi MC, et al. NEJM 2007.
Table 4. Recommendations for detection of delayed onset extra-pulmonary manifestations of sarcoidosis after initial negative screening. From Am J Respir Crit Care Med. 2020 Apr 15; 201(8): e26–e51.

- **Pulmonary** – There is no data on the frequency of specific testing for monitoring of patients with sarcoidosis. Patients with more significant symptoms or disease severity/progression should be monitored at more frequent intervals with PFTs. Consider repeat CT to be certain that all nodules are only due to sarcoidosis.

- **Cardiac**– history of shortness of breath out of proportion to lung involvement or palpitations should prompt further evaluation. EKG should be performed annually – if either EKG abnormal or symptoms present, recommend further evaluation with echocardiogram and/or 24-hour Holter monitor. Cardiac MRI with and without gadolinium looking for delayed gadolinium enhancement or a cardiac PET can also be used if there is suspicion for cardiac sarcoid. Echocardiography is a useful tool to screen for sarcoidosis associated pulmonary hypertension. (Duon H et al Clin Pulm Med 2018)

- **Ophthalmic**– red eye or dry eyes – will need ophthalmic consultation to rule out uveitis.

- **CNS**– History of strokes, seizure or problems with memory should prompt further evaluation.

- **Hepatic**– Elevations in ALP. AST, ALT, T. Bili should be screened for and monitored.

- **Splenic**– Palpation of spleen, CBC

- **Extrapulmonary lymph nodes**– full lymph node examination.

- **Skin**– full body examination

- **Neurologic**– full examination– MRI to look for delayed gadolinium enhancement.

- **Bone**– cystic lesions are not uncommon but would only to scans if there were specific complaints.

- **Bone Marrow**– CBC, Bone marrow biopsy

- **Renal**– BUN, Creatinine
**ACTIVE DISEASE**  
(check every 3-6 months)  
- History and physical  
- PFTs  
- 6MWT  
- Eye exam (if on hydroxychloroquine)  
- Labs based on site of disease activity  

**ACTIVE DISEASE**  
(check annually)  
- CBC, CMP (including Calcium and LFTs)  
- Vitamin D  
- EKG  
- Eye exam  
- +/- chest imaging  

**INACTIVE DISEASE**  
(check every 12-18 month)  
- History and physical  
- PFTs  
- 6MWT  
- CBC, CMP (including LFTs and Calcium)  
- Vitamin D  
- EKG  
- Eye exam

Figure 4. Suggested ongoing monitoring of patients with sarcoidosis diagnosis. Individual practice will likely vary given lack of good studies to guide frequency and utility of screening and follow up studies. Adapted from King TE, et al. UptoDate 2018.

**Question 5: Should you treat Ms. Hernandez? How does treatment vary depending on the extent of disease and organ involvement? When should you consider steroid sparing therapies?**

Most patients with sarcoidosis do not require treatment. The decision to treat is typically based on symptoms, radiographic findings, and PFTs. Generally speaking, patients should be treated if there is evidence of active inflammation, bothersome symptoms related to organ involvement, impaired organ function or the patient is at risk for progressing to fibrosis. Wells Law (put forth by Dr Athol Wells) outlines that treatment for sarcoidosis should only be considered to avoid danger (organ dysfunction/death) or to improve quality of life (Baughman et al Sarcoïdosis Vasc Diffuse Lung Disease 2017). Imaging findings suggesting sarcoidosis activity include nodules, recurrent consolidation and occasionally ground glass opacities. Given that Ms. Hernandez has moderate symptoms and moderately severe impairment in her PFTs, starting systemic steroids should be considered, usually in a range of 20-40 mg daily at the start. For her, we might opt for 20 mg with a planned taper over the next several months given the modest degree of impairment but again there will be variability by provider preference. The goals of management are to prevent or control organ damage, relieve symptoms and improve patient quality of life. The suggested algorithm for the treatment of pulmonary sarcoidosis is outlined in figure 5 below, borrowed from the Foundation for Sarcoidosis Research Treatment Guidelines. Many of the therapies however also have a host of side effects. See Table 5 below. Note that treatment algorithms vary with the presence of extrapulmonary sarcoidosis. The mechanisms of current and experimental therapies used for sarcoidosis are outlined in Figure 6.
Figure 5. Suggested Physicians Treatment Protocol from the Foundation for Sarcoidosis Research. https://www.stopsarcoidosis.org/physicians-and-investigators/treatment-protocol/

<table>
<thead>
<tr>
<th>DRUG</th>
<th>DOSAGE</th>
<th>MAJOR TOXICITY</th>
<th>MONITORING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisone</td>
<td>5-40mg daily</td>
<td>Diabetes, hypertension, weight gain, cataracts, glaucoma</td>
<td>Blood pressure, weight, glucose if clinically indicated. Osteoporosis and bone density checks</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>200-400mg daily</td>
<td>Ocular, hepatic, cutaneous</td>
<td>Eye examination every 6-12 months</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>5-20mg weekly</td>
<td>Hematologic, hepatoxic, pulmonary</td>
<td>CBC, hepatic and renal function every 1-3 months</td>
</tr>
<tr>
<td>Azathioprine*</td>
<td>50-200mg daily</td>
<td>Hematologic, gastrointestinal</td>
<td>CBC, hepatic and renal function every 1-3 months</td>
</tr>
<tr>
<td>Leflunomide*</td>
<td>10-20mg daily</td>
<td>Hematologic, hepatoxic</td>
<td>CBC, hepatic and renal function every 1-3 months</td>
</tr>
<tr>
<td>Mycophenolate</td>
<td>500-1500mg twice daily</td>
<td>Hematologic, gastrointestinal</td>
<td></td>
</tr>
<tr>
<td>Infliximab</td>
<td>3-5mg/kg initially, two weeks later, then every 4-8 weeks</td>
<td>Allergic reactions, increased risk for infections, especially tuberculosis, worsening congestive heart failure, possible increased risk for malignancy</td>
<td>PPD prior to initiating therapy, withhold drug in face of active infection</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>40-80mg every 1-2 weeks</td>
<td>Allergic reactions, increased risk for infections, especially tuberculosis, worsening congestive heart failure, possible increased risk for malignancy</td>
<td>PPD prior to initiating therapy, withhold drug in face of active infection</td>
</tr>
</tbody>
</table>

Definitions: mg=milligrams; kg=kilogram; CBC=complete blood count; PPD=purified protein derivative, skin test to diagnose tuberculosis.

* See text for initial monitoring

Figure 6. Current and investigational treatments for sarcoidosis based on pathogenesis. Borrowed from Gerke et al Front Immun 2020

**Question 6: What drugs can cause sarcoidosis like reactions?**

Immune checkpoint inhibitors, highly active retroviral therapy, interferons and Tumor necrosis factor-a antagonists
References

4. Young, Sperry, Hachamovitch,Update on Treatment in Cardiac Sarcoidosis, Curr Treat Options Cardio Med (2017) 19:47
5. Mayock, Bertrand, Morrison, Scott, Manifestations of Sarcoidosis American J of Medicine (1963) 35:67-89
6. Chopra, Nautiyal, Kalkanis, Judson, Drug-Induced Sarcoidosis-like Reactions, Chest 2018 Apr 24