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Review Article

Sarcoidosis: Review of Diagnosis and Treatment

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Abstract

Background: Sarcoidosis is a systemic heterogenous granulomatous disease of unknown etiology that results in inflammation of pulmonary and extrapulmonary sites. In a minority of patients it can result in fibrosis and permanent organ damage. Most commonly mentioned causes of sarcoidosis include atypical mycobacterium, proprionobacterium and inorganic dusts. Once exposed to an organic or inorganic, an Antigen Presenting Cell (APC) prepares and presents the antigen to a T cell and its respective HLA locus. In a susceptible person, this provides cytokine production, differentiation into T helper cells and provokes an immune response that in its early stages is allayed by corticosteroids or other immunomodulatory agents. In the majority of patients appropriate immunomodulatory therapy will control the disease and prevent progression. However, in 20-25 % the disease can progress and lead to organ damage or compromise and fibrosis. Sarcoidosis is a relatively common disease with an incidence of 2.3-17.8 per 100,000. It is 2-4 times more common in African Americans than Caucasian Americans with the mean age of onset of 45-50 years of age. Unlike autoimmune rheumatic disease the disease occurs almost as commonly in men than women.

Sources: A Medline, Pub Med review from 1999-2021.

Spectrum of Disease: Sarcoidosis occurs in 90-98 % of patients during the course of their disease. Eleven to twenty two percent of patients have involvement of either the liver, Skin, ocular (uveitis), Lymph nodes and spleen. The upper airway, liver, CNS and heart comprise <10% of cases each and the bone, joints/ muscle, and hypercalcemia < 5%.

Diagnosis: With the exception of Lofgren's and Heerfordt'syndromes the presence of non-caseating/necrotizing granuloma must be present on biopsy of at least one site and mycobacterial or fungal infections or malignancy must be ruled out. If clinically suspicious, Skin and peripheral lymph nodes are the least invasive areas for biopsy and if hilar or mediastinal nodes are suggestive, an EBUS approach is recommended. In organs such as the heart and CNS where biopsy is either insensitive or invasive, a Cardiologist and Neurologist in concert with a Rheumatologist can make a probable diagnosis based on clinical presentation, PET or MRI and exclusion of alternative diseases.

Treatment: The use of corticosteroids depends on the organ or organs involved, the trend and tempo of their involvement and the potential for reversibility. Patients with lung involvement, normal pulmonary function tests and limited CT appearance may be observed without steroids. If uveitis is present and isolated to the anterior chamber, ophthalmic steroids are indicated; systemic steroids are reserved for panuveitis. Cutaneous sarcoid can be treated with topical steroids, colchicine or a CLEAR antibiotic regimen first. A starting dose of 20-40 prednisone is recommended for patients with organ involvement deemed to be of significance or likely to progress. For example moderately severe respiratory sx, abnormal pulmonary function tests or CT images, extensive lymphadenopathy hepatic inflammation, hypercalcemia or symptomatic upper airway, osseous or musculoskeletal involvement.

Sarcoidosis involving the cardiac or neurologic systems, should be treated with 60 mg of prednisone or 1 mg/kg prednisone or IV solumedrol, depending on the severity and trend and tempo of the affected organ. A Cardiologist or Neurologist should partner with a Rheumatologist in management of cardiac or neurosarcoid. Imaging and clinical findings should guide duration of therapy.

For patients who are unable to taper corticosteroids, methotrexate if the preferred first steroid sparing agent. Infliximab is the most commonly prescribed drug that is added to methotrexate for disease refractory to methotrexate.

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Key points:

- Sarcoid is a granulomatous disease of unknown etiology whose appearance is most common in the lung, lymph nodes, spleen and uveal tract.
- With the exception of Lofgren's and Heerfordt' syndromes the presence of a granuloma (95% caseating) in a tissue biopsy of the affected organ with the exclusion of fungal, mycobacterial or malignant causes is necessary for the diagnosis.
- In cases of suspected cardiac or neurosarcoidosis noncaseating granuloma found in another location together wih MRI or PET imaging. a probable clinical presentation and agreement with a Cardiologist or Neurologist and Rheumatologist, can be used to make a diagnosis in the affected organ.
- Observation alone or topical or ophthalmic steroids may be used in limited pulmonary disease, skin sarcoid or anterior uveitis.
- Corticosteroids in a starting dose of 20-40 mg prednisone or equivalent are recommended for organ involvement. A starting dose of 20-40 prednisone is recommended for for patients with organ involvement deemed to be of significance or likely to progress, especially pulmonary, hepatic, lymphatic and for hypercalcemia. Dose should be maintained for 4- 8 weeks.
- Prednisone 60 mg or 1 mg/kg or higher dose solumedrol are indicated for Neuro or Cardiac sarcoid. The disease should be monitored by a Neurologic or Cardiologic in partnership with a Rheumatologist. Imaging and clinical symptoms can be used to guide duration of therapy.
- In an inflammatory phase, sarcoidosis is highly responsive to prednisone such that steroid failure should raise concern about an alternative diagnosis.
- In patients who are corticosteroid dependent or intolerant of optimal doses, methotrexate is the preferred first steroid sparing agent. Leflunomide, mycophenolate and azathioprine are possible if methotrexate is not tolerated. If methotrexate is ineffective in allowing disease control and steroid tapering (optimally < 5mg prednisone within 3 months), infliximab is added. Subcutaneous Adalimumab is an alterative TNF inhibitor. Other biologics and JAK inhibitors are under investigation as steroid sparing alternative.

Definition

Sarcoidosis is a steroid responsive, systemic heterogenous granulomatous disease of unknown etiology that results in inflammation of pulmonary and extrapulmonary sites. In a minority of patients it can result in fibrosis and permanent organ damage [1-5].

Etiology

As the lungs are the most common target of sarcoidosis it is hypothesized that an organic or inorganic antigen is likely inhaled and provokes an immune response in bronchiolar macrophages [6-11]. Both mycobacterium and proprionobacterium genetic signatures have been found in lymph nodes and whole blood of patients with sarcoidosis and sarcoid granulomas have been produced by these bacteria in several animal models(6,7,8,9) Case control studies have shown an increased incidence of sarcoidosis in debris workers and firefighters from the World Trade Center disasters and in silica exposed workers. Similar studies have found an increased incidence in agricultural workers exposed to insecticide and microbial bioaerosols and in industrial workers exposed to metal dust. Odd ratios in these studies range from 1.2-4 [11-15].

Epidemiology: The incidence of sarcoidosis ranges from 2.3 to 17.8 new cases per 100,000 per year with the peak age of onset between 35 and 55 years of age and a mean age of 45-50. The rate is 2 to 4 times higher in African Americans when compared to Caucasians. The incidence in women ranges from 45-63% [14,16-18].

Pathogenesis

In the presence of susceptible HLA loci, an unidentified substance is recognized by Antigen Presenting Cells (APCs) that produce cytokines and recruit and differentiate T lymphocytes into TH1 and TH2 cells. These lymphocytes then produce more cytokines that simulate the production of granulomas of which 95% are noncaseating or non-necrotizing. These granulomas produce additional cytokines such as Tumor Necrosis Factor alpha (TNF) and gamma interferon which evoke systemic inflammation, most often centered in the lungs and lymph nodes and less commonly in the uveal tract of the eye and the skin. In 10-20% of patients the inflammation can progress to fibrosis most commonly in the lungs, uncommonly in the heart or nervous system [19-23].

Spectrum of Disease: The lungs are initially involved or subsequently involved in 91-98 % of patients with the most common presentation being a dry cough with mild to moderate dyspnea on exertion, often accompanied by atypical chest pain, fatigue and malaise [24-28]. Fifty to sixty percent of patients have more than one organ involved [25]. The most common sites of extrapulmonary

disease, in order, are extra thoracic lymph nodes or spleen (22.8%), skin (20.5%) [29], eye-uveitis (12.4%) [30], liver (11.5%) [31], neurologic (8%) [33], ENT/parotid/salivary (6.7%) bone/joint (4.5%) [34-36] cardiac (3.7%) [32] hypercalcemia (3.5%), bone marrow (3.4%), renal or muscle (<2%) [25].

Diagnosis

The diagnosis of sarcoidosis is made on a clinical foundation, supported by tissue pathology. Although there are guidelines for making the diagnosis they are consensus not evidence based. The presence of noncaseating or non-necrotizing granulomas is a necessary criteria for diagnosis with two exceptions: Lofgren's and Heerfordt's syndromes [37]. Lofgren's is an acute illness characterized by erythema nodosum, pauciarticular large joint arthritis/periarthritis and bilateral hilar adenopathy. Heerfordt's is acute uveitis, parotitis, fevers and facial nerve palsy [1,37]. The Angiotensin Enzyme Inhibitor (ACE) has sensitivities ranging from 41-70 % (mean 58%) and a specificities of 70-80%, the latter depending on the magnitude of elevation beyond the normal range [39-41] Likewise, other serum biomarkers, IL-2, chitotriosidase, Lysozyme and KL-6 have not proven to be of sufficient accuracy to make a diagnosis [42,43].

The presence of noncaseating/non-necrotizing on tissue bx with the concomitant elimination of mycobacterial, fungal infections and malignancy as alternative explanations is sufficient for the diagnosis of sarcoidosis. Caseating/necrotizing granulomas are found in approximately 5% of cases of sarcoidosis but prompt a rigorous investigation into infectious or malignant causes of granuloma formation. If hilar or mediastinal adenopathy is demonstrated on a CT of the chest, an endoscopic biopsy (EBUS) of the affected area is recommended in lieu of a mediastinoscopy or VATS procedures [4]. As sarcoid can be detected in skin and extra thoracic lymph nodes in up to 30% of patients, a biopsy from one of these sites confirms the diagnosis obviating the need for a biopsy of intrathoracic lymph nodes [4,38,39]. The diagnosis of cardiac or neuosarcoidosis requires a different approach. Cardiac disease classically present as a serious brady or tachyarrhythmia, (AV nodal block or ventricular tachycardia) or a non- ischemic cardiomyopathy. The diagnosis is confirmed by either a cardiac MRI illustrating focal delayed enhancement or a PET scan showing focal cardiac avidity in a non -ischemic distribution in conjunction with the presence of noncaseating granulomas in a non- cardiac location. Endomyocardial biopsy is insensitive because of the focal or patchy distribution of the granulomas [45-48]. Neurosarcoidosis can be diagnosed with a positive tissue biopsy outside of the neural network but only if other etiologies for the neurologic diagnosis are ruled out and the neurologic involvement is leptomeningeal or a cranial neuropathy, the former of which shows gadolinium enhancement [33,44]. Brain or leptomeningeal biopsy is reserved for cases where the Neurologist requests it [44]. In a minority of cases sarcoid uveitis has characteristic findings on Ophthalmologic examination that allow for a diagnosis without tissue biopsy [30]. As granulomatous hepatitis has a wide differential diagnosis, the diagnosis of hepatic sarcoid requires agreement with a hepatologist or demonstration of noncaseating granulomas in another organ [31].

Treatment: First determine the extent of disease [1,4,49]. As 30-60 % of patients have sarcoid in more than one organ, it is necessary to define the extent of the disease. In order to determine whether therapy is indicated it is advisable to first search for extra thoracic disease [49-51]. A neurologic and cardiac history and exam should screen for central or peripheral nervous disease, a cardiomyopathy or arrhythmias. An Opthalmologist should search for uveitis. Initial diagnostic studies should include a metabolic panel, CBC and EKG. If there is suspicion of cardiac or neurologic disease a specialist should be consulted to determine the need for advanced imaging (echocardiogram, Cardiac MRI, PET scan, Brain/spinal cord MRI, CSF exam) [4].

Second, assess whether observation without systemic steroid therapy is possible [51,52-61]. if disease is found only in the lungs a pulmonologist should assess the patient and with the assistance of Pulmonary Function Tests and a chest CT decide whether observation will substitute for corticosteroids. For example, if pulmonary disease limited to hilar adenopathy with no suspicion of interstitial or reactive airways disease and no or negligible pulmonary symptoms, observation without treatment is recommended [1,4,61-69]. In cases of isolated anterior uveitis, ophthalmic steroids can be used to control the disease but if posterior uveitis or retinal disease is are present, systemic steroids are indicated [70]. Isolated dermatologic sarcoid can be managed with topical steroids, colchicine or an CLEAR regimen (Combination Levofloxacin, Ethambutol, Azithromycin & Rifampin) [29].

Third if immunomodulatory therapy is indicated, corticosteroids should be started in a dose of 20-40 mg prednisone or its equivalent in symptomatic sites other than neurologic or cardiac [1,57,58,67]. In these cases 60 mg or more of prednisone should be given [53-55]. Testing for latent tuberculosis and assessment of bone health should be performed. In doses of 20 mg or more of prednisone or its equivalent, prophylaxis for Pneumocystis Jirovecci is routine at Stanford. In my experience and that of many colleagues, a very high proportion of patients will show improvement in disease manifestations within 2-6 weeks of initiating steroid therapy. Failure to respond should prompt a reconsideration of the diagnosis.

There are no evidence based guidelines, nor consensus on the duration of steroid therapy but there is general agreement that the starting dose should be maintained, if possible, for at least 4-8 weeks [51,52,58,59]. Depending on the severity of the disease and its trend and tempo, tapering should begin as soon as possible with dose reduction of 10-20 % every two weeks. One should remember that there can be a lag between a prednisone dose reduction and a relapse that may not become apparent for a number of weeks [63]. A minority of patients will be able to taper off steroids entirely and can be observed for disease recurrence. However, the majority will have disease recurrence off steroids or be unable to taper the dose of prednisone or its equivalent to less than 5 mg without a flare. Assuming that there is not an alternative explanation for a patients' symptoms, non -adherence or steroid side effects [63], if a patient cannot taper to 5 mg or less within a period of 2-3 months, then steroid sparing agents must be considered [51,52,57,58,61]. Although there are insufficient controlled trials to guide therapy, methotrexate is the most effective and commonly prescribed initial non-steroid immunomodulatory agent chosen. Should methotrexate fail to maintain disease stability with steroid reduction, TNF inhibitors are added to methotrexate or substituted if methotrexate is not tolerated. IV infliximab is the best documented of this class of biologics,

although adalimumab also has shown efficacy [56]. For patients intolerant of methotrexate but in whom the clinician believes an oral immunosuppressive should be used in combination with an anti-TNF agent, azathioprine, leflunomide or mycophenolate are have been effective in cohorts, cases or small groups [53,58,59]. Other steroid sparing agents such as the JAK inhibitor tofacitinib, the anti-TNF golimumab, IL- 6 inhibitors and the IL 12/23 inhibitor ustekinumab have shown preliminary success in uncontrolled trials [61,63,65,66].

Follow-up intervals for sarcoid are not standardized. However, one should keep in mind that as many as 50% of patients will have a remission in 3 years, and 66% in 10 years, and yet, approximately 1/3rd of patients will have complications of vital organs (lungs, heart, CNS, hepatic, renal) with progressive disease [25,27,50,67,69]. One should also remember that the status of pulmonary, ocular, cutaneous and hepatic sarcoid sarcoid are easier to monitor than cardiac or neurologic disease and that involvement of three of more organs, stage 3 or 4 chest radiograph, posterior uvieits, age >40, African American heritage, hypercalcemia, the extent of cardiac or neurologic disease, lupus pernio and >6 months are risk factors for disease recurrence [25-27,37,39,50].

Summary: Sarcoidosis is a systemic steroid responsivegranulomatous disease of unproven etiology that presents most commonly in the lung and uveal tract, extrathoracic lymph nodes, spleen and skin whose diagnosis is made by the presence of noncaseating/necrotizing granulomas in the absence of mycobacterial, fungal infections or malignancy. It affects more than one organ in 30% of patients and is recurrent or progressive in 1/3rd Although neurologic and cardiac disease is present in only about 12% of patients MRI or PET imaging and a characteristic clinical presentation are necessary to make the diagnosis. Patients with disease that is limited to the skin or anterior uveal tract can be treated with topical or ophthalmic steroids and patients with limited, symptomless or minimally symptomatic, non progressive pulmonary disease can potentially be observed without therapy. All other patients respond well to doses of prednisone ranging from 10-40 mg (skin, pulmonary, ENT) to 60 mg or more (cardiac, neurologic). The majority of patients however, are unable to taper off steroids and will require steroid sparing immunomodulatory therapy, most commonly methotrexate and/or infliximab. The disease is progressive and results in fibrosis and permanent organ dysfunction in a minority of patients, most commonly when there is significant involvement of the heart, CNS, lung or posterior uveal tract and in the presence of risk factors.

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