

SARCOIDOSIS

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Definition:

Sarcoidosis is a systemic granulomatous disease that primarily affects the lungs and lymphatic systems of the body. A diagnosis of the disorder usually requires the demonstration of typical lesions in more than one organ system and exclusion of other disorders known to cause granulomatous disease.

Hutchinson in 1877 first time described a case of sarcoid.

Epidemiology:

The disease affects both sexes and all races and ages. There is predilection for adults less than 40 yrs of age, peaking 20 to 29 years old. A second peak has been reported in women's more than 50 years of age.

In the US the life time risk for white 0.85% and 2.4% for black.

The highest prevalence rates are reported in Swedes, Danes and US blacks, and is rarely reported in Spain, Portugal, India, Saudi Arabia and South America.

Etiology:

1) Genetic factors with reports of familial cluster, possible due to shared exposure or class I HLA-A1 and B8 and Class II HLA-DR3.

2) Environmental Factors implicated could be ;Viruses (herpes, EBV, retrovirus, coxsackie B, CMV Bacteria (Borrelia burgdorferi, Propionibacterium, MTB, other mycobacteria, Mycoplasma), inorganic Aluminum, Zirconium, Talc, organic Pine tree pollen, and Clay.

3) T-Cell receptors: with possible role for T cells with restricted TCR usage.

In animal models highly restricted TCR V gene can mediate connective tissue disease.

1) Immunology: with well reported CD4 cells dysregulation and dysbalanced IFN-gamma, IL-2, TNF

alpha, IL-12, IL-15 and growth factors.

Clinical Presentation:

1) Non-Specific Symptoms:

* Fever, fatigue, malaise and weight loss.

* More frequent in African Americans and Asian Indians

* Fever of Unknown origin.

2) Organ Involvement:

1- Lungs:

* Involved in more than 90% of patients with sarcoidosis, with symptoms such as dyspnea, dry cough and chest pain, hemoptysis, Clubbing and Lung crackles.

* Parenchymal lung disease (larynx, trachea, bronchi) may lead to airway obstruction and bronchiectasis, airway hyperactivity.

/In 5% pleural effusion (Lymphocytic), chylothorax, pneumothorax, pleural thickening, lymph node calcification and cavity formation can occur.

1- Chest Radiographic Staging:

Stage Findings

0 Normal Chest X-ray

I Bilateral hilar lymphadenopathy (BHL)

II BHL plus pulmonary infiltrations

III Pulmonary infiltrations (without BHL)

IV Pulmonary fibrosis

2- Cardiac:

* Involvement in about 5 %, but autopsy incidence is higher.

* Can present as benign arrhythmias, high-degree heart block to sudden death. 24 hour Holter may reveal VT, heart block or V. ectopic beats and Doppler Echocardiogram showing diastolic dysfunction.

* Thallium-201 can demonstrate reversed segmental contraction abnormalities. And endomyocardial biopsy will show granuloma.

3- Skin:

* Cutaneous involvement in 25%.

* Possible presentation is Erythema Nodosum (EN), Lupus pernio. Plaques, maculopapular eruptions, subcutaneous nodules, changes in old scars, alopecia, and hypo- and hyperpigmented areas.

* Acute form of the disease is called Lofgrens syndrome with fever, BHL, EN and Arthralgia.

4- Ocular:

* Occur in 11 to 83%.

* Uveitis most common.

* Any part can be involved.

* Acute anterior uveitis.

* Chronic uveitis, glaucoma, cataract and blindness.

* Lacrimal gland enlargement, keratoconjunctivitis sicca, dacryocystitis and retinal vasculitis.

5- Liver:

* Granuloma found in 50-80% of liver biopsy.

* Liver palpable in 20%.

* Asymptomatic patients with mild LFT abnormalities do not need treatment.

* Corticosteroids may improve liver dysfunction.

6- Lymphoid System:

* 1/3rd palpable peripheral lymph nodes.

* Cervical, axillary, epitrochlear and inguinal.

* Splenic enlargement, Cysts.

7- Neurosarcoidosis:

* Less than 10%.

* Base of the brain.

* Cranial nerves (facial nerve), Hypothalamus and pituitary.

* Lesion occurs early and responds to treatment.

- * Chronic course, space-occupying lesion, peripheral neuropathy, neuromuscular involvement.
- * Gadolinium-enhanced MRI.
- * CSF, lymphocytosis, proteins, ACE, CD4/CD8 ratio.

8- Musculoskeletal:

- * Joint pain 25 to 39%.
- * Knees, ankles, elbow, wrists and small joints of hands and feet.
- * Synovial or muscle biopsy.

9- Endocrine:

- * Hypercalcemia 2-10%, hypercalciuria three times more common.
- * Dysregulated production of 1.25-(OH)₂-D₃ (calcitriol)
- * Nephrocalcinosis, renal stones, and renal failure.
- * DI, pituitary or hypothalamus involvement.
- * Hypothyroidism, hyperthyroidism, adrenal suppression and anterior pituitary involvement.

10- Gastrointestinal Tract:

- * Less than 1.0%
- * Stomach, Esophagus, appendix, rectum, pancreas.
- * May mimic Chrons disease, TB, or Fungal infection.

11- Hematologic:

- * Anemia in 4 to 20%.
- * leukopenia in 40%.

12- Parotid Gland:

- * Unilateral or bilateral parotitis in 6%.
- * Self-limiting in 40%.
- * Heerfordts syndrome: fever, parotid enlargement, facial palsy and anterior uveitis.

13- Kidney:

- * Interstitial nephritis.
- * Nephrolithiasis, Nephrocalcinosis.

*** Diagnosis:**

- * Transbronchial Biopsy 40% to 90% with 4 to 5 biopsies.
- * Open Lung biopsy
- * Other sites such as skin, lip, lymph nodes
- * Lofgrens syndrome: fever, EN, arthralgia and bilateral hilar lymphadenopathy.
- * In BAL; CD4/CD8 ratio greater than 3.5 sensitivity 53%, specificity 94%.
- * Gallium scan o ACE level
- * PFTs - DLCO, VC, Restrictive and obstructive
- * CT Chest

-In atypical clinical or X-ray presentation.

-Complications, bronchiectasis, aspergilloma

-Normal Chest X-ray

*** Pathology:**

- * Discrete, compact, noncaseating epithelioid cell granuloma.
- * Epithelioid cell granuloma consists of mononuclear phagocytes (epithelioid and giant cells), lymphocytes.
- * Central portion CD4 cells, Peripheral zone CD8 cells.
- * Tight, well formed granuloma, rim of lymphocytes and fibroblast in the outer margin, perilymphatic interstitial distribution.

*** Patient Surveillance:**

- * Stage I follow up every 6 months.

- * Stage II, III, IV every 3 to 6 months.

- * Therapy in severe, active or progressive disease.

- * Persistent stable asymptomatic Stage I: no therapy (annually)

- * Stage II, III, IV: indefinitely (at least annually)

*** Management:**

The management of sarcoidosis is not straightforward due to difficulties in the decision of when and how to start therapy, when to stop therapy, and what drug to use, but as a consensus therapy has to be started in symptomatic patients, (progressive respiratory symptoms, cardiac, CNS, hypercalcemia, eye ...).

Drugs used are:

- * Corticosteroid.

- * Cytotoxic drugs:

-Methotrexate.

-Azathioprine.

-Cyclophosphamide.

- * Immunomodulators:

-Other Agents.

- Clofazimine.

- Minocycline

In asymptomatic patients, no treatments, but observation is indicated.

1- Corticosteroids:

Despite the widespread idea about treating sarcoidosis with steroid and of it being the drug of choice to start with, there have been recently many questions about the real effect and the change of natural history of disease progression.

But until new knowledge and new studies are out to solve these problem steroids remain the first line drugs in sarcoidosis.

In meta-analysis, included randomized clinical trials, with systemic steroid for up to 18 months led to improvements in X-Ray and in DLCO, but no improvement in FVC.

In another double blind, placebo controlled, multicenter trial, systemic corticosteroids for 3 months, followed by 15 months of inhaled budesonide led to improvement for those treated for 18 months, these patients followed for 5 years.

2- Cytotoxic Drugs:

Like Methotrexate, Azathioprine, Cyclophosphamide or Combination therapy.

1- Methotrexate, is used as second line agent in a dose of 10-25 mg/wk.

In a double blind, randomized trial comparing Methotrexate and prednisone with placebo controlled group, the use Methotrexate and prednisone led to a reduction in prednisone dose, with difference in side effects in this study.

Commonly reported side effects nausea, mucositis, Hematologic, HP and hepatotoxicity.

The use of MTX Useful in treating sarcoidosis with progressive pulmonary disease, ocular disease, pediatric sarcoidosis, cutaneous sarcoidosis and neurosarcoidosis. Close follow up of CBC, LFT's.

2- Azathioprine

In chronic sarcoidosis is used in dosage 50-200 mg/d, in two series have shown benefit with or without prednisone.

Side effects Nausea, vomiting, mucositis, Hematologic, teratogenic.

3- Cyclophosphamide: Cyclophosphamide is reserved for refractory cases, e.g. neurosarcoidosis, in a dose of 50-200 mg/day.

Side effects are hemorrhagic cystitis, leucopenia and in long term use skin malignancies.

3- Immunomodulators:

Which can alter the immune system or block cytokine effects, such as Chloroquine, Hydroxychloroquine

They are effective for cutaneous disease, hypercalcemia, neurologic disease, and may slow the decline in FEV1, DLCO.

1- Chloroquine may cause irreversible retinopathy and blindness, and eye exam every 3 to 6 months is recommended. So treatment is limited to 6 months.

2- Hydroxychloroquin may decrease Insulin degradation in the liver, decreasing gluconeogenesis, which makes it good choice in Diabetics with mild to moderate sarcoid. It also has a lower risk of ocular toxicity.

4- Tumor Necrosis Factor Blockers:

TNF enhances alveolar macrophages activity in active sarcoid, and will lead to increase granuloma formation, and disease activity.

TNF secretion (or action) can be decreased by the use of various drugs such as corticosteroids, MTX, Pentoxifylline, Thalidomide and Infliximab.

1-) Petoxifylline: which can decrease TNF secretion, has been shown to induce high rate of remission in acute pulmonary sarcoid, but its utility in chronic sarcoid is not proven yet.

2- Thalidomide: which can decrease TNF and IL-12 secretion has been shown to be very effective in chronic cutaneous sarcoid and in an open label study in lupus pernio for 4 months showed Improvement but not complete resolution.

3- Infliximab: (Murine monoclonal antibody): in a case series two with lupus pernio one with pulmonary sarcoid showed improvement.

Yee et al. reported case series of refractory sarcoid induced to remission with Infliximab and then thalidomide to control the disease. All cases have been treated with other agents.

Toxicity for 1 year was low, but long term effects are not known yet. Important to mention is the increased rate of TB (with extrapulmonary TB in the majority).

5- Other Agents:

1- Clofazimine: a single case report of refractory laryngeal sarcoidosis, in a dose 100mg/day, showed good response.

2- Minocycline: is reported to be effective in cutaneous sarcoidosis.

In eight of twelve patients Minocycline induced a complete response and an additional two partial response for their skin lesion.

Conclusion:

* Sarcoidosis is a multisystem granulomatous disease that mainly affects the lungs.

* 1st peak 20 - 29 years, 2nd peak 50 years.

* Etiology? Familial clusters, shared exposure (theories).

* Staging is Chest radiographic, but not functional.

* Surveillance of Stage II, III, IV indefinitely.

* Difficulties in management include the decision of how and when to start therapy, when to stop therapy, and what drug to use.

* Treatment includes Corticosteroids, Cytotoxic, Immunomodulators and other agents.

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