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Sarcoidosis: An Overview

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SUMMARY

Sarcoidosis is a multi-system granulomatous diseases of undetermined etiology characterized by activation of lymphocytes and mononuclear phagocytes at the site of the disease (1). Seen most often between 30-40 years of age, it can effect any race, though less common in tropics. It involves lungs in 80-90% of cases (2), although it is a multi-organ disease and can present to any of the medical or surgical discipline (3). In areas endemic for Tuberculosis like Pakistan there may be lot of difficulty in excluding Mycobacterial infection, since both the diseases have similar clinico-radiological, biochemical and pathological features (4). Clinical and epidemiological features favor the hypothesis that it results from environmental exposure, possibly infective agents. An updated review of the subject is presented.

Key Words: Sarcoidosis, Granulomatous Disease, Lupus, Interstitial Lung Disease.

INTRODUCTION

Going through the chronology of historic events it seems that clinically Sarcoidosis has been recognized for more than one hundred years.

First clinical description of the disease came as a case of Mortimer's malady in 1889 by Hutchison. In 1893 Besniers described facial lesion lupus pernio as a variant of lupus erythematosis. In 1899 Boek described non-caseating granuloma in a benign Sarkoid (sarcomatous) skin disease. In 1914 Shauman (Swede) described the disease as a systemic illness. Thirty five years later in 1950 Kveim silt Bach reaction provided support for the pathogenesis. Three years later Lofgren described bilateral hilar enlargement as early and favorable signs. Only during the last twenty years studies on cell and molecular biology has explained cellular mechanism of granulomas, however etiology still remains obscure.

Epidemiology

Prevalence is unreliable since many people remain asymptomatic[5]. In areas endemic for tuberculosis it is not possible to have accurate diagnosis. It occurs in all races. In Western countries like USA it is more common among blacks (10-17 times), more frequent in women, and about 70% in age group 20-45 years. Erythema nodosum is more common in young age, whites and childbearing women; while chronic disease process, like lupus pernio is more common in blacks.

Aetiology

It is a transmissible disease as is evident from Kveim reaction. Mycobacterial nuclear components have been isolated from sarcoid lesions[6]. High antibody titer against Ebstein Barr virus, human lymphotropic virus-I, para-influenza, cytomegalo virus, Herpes, Rubella virus have been isolated, however no virus has been cultured. Clusters of sarcoid cases have been observed in relation to seasonal, occupational or familial factors[7]. Generalized immune dysregulation is evident from positive antinuclear antibodies, rheumatoid factor, increased immunoglobulin and immune complexes. Genetic susceptibility is probably polygenic and genetic markers (like HLA) are not consistently observed.

Pathogenesis

Epitheloid cell granulomas which are discrete, noncaseating and in different stages of development are the hall mark of the disease. Mature

macrophages with CD4 and CD8-positive lymphocytes are present within the granulomas; mostly seen in perivascular and peribronchial areas rich in lymphatics. Interstitium is frequently infiltrated by mononuclear (lymphocytes) cells, together with disruption of type-I epithelial cell basement membrane. Granulomatous inflammation results from interaction between CD4+T cells, mononuclear phagocytic cells, fibroblasts, B cells, dendritic cells and other cells which in turn are regulated by cytokines and chemokines released by immune-competent cells, dominantly gamma interferon and interleukein-12 (IL 12).

Clinical features[8]

Any organ of the body may be affected (Table-1) though lungs and lymph nodes are involved in >90% of the cases. About two third of the total patients are picked up through routine chest radiograph showing bilateral hilar lymphadenopathy while they are asymptomatic. A white patient may present with lung infiltrates while still asymptomatic. Sarcoidosis and idiopathic fibrosing alveolitis are the two most frequent interstitial lung diseases[9]. Eye and skin involvement is seen in 20% of the cases. During the course of illness 1/3rd of the patient may get spontaneous remission, another 1/3rd require drugs for induction of remission and remaining 1/3rd run a lingering and progressive course. Clinical presentation may be acute, sub acute (< 2 year duration) or chronic (symptomatic> 2 years.). Remissions and relapses are characteristic during the course of illness[10].

Actue sarcoid

This presents with abrupt onset of erythema nodosum, fever, polyarthritis or uveitis (Lofgren's Syndrome), 10% of these patients have no chest X-ray abnormality, seen more often in whites, cary good prognosis and resolves within 6 months.

Pulmonary sarcoid

Chest symptoms occurs in 40-60% of patients; which are mainly dry cough and exertional dyspnoea which is usually progressive. Fibrocystic sarcoidosis is associated with, exertional dyspnoea which is usually progressive, productive cough hemoptysis, bronchiectasis and recurrent chest infection. Chest pain is quiet common but tightness and wheezing is relatively uncommon. Cough and wheezing usually do not settle with bronchodilators. In the absence of interstitial lung disease pulmonary hypertension and corpulmonale can complicate, consequent of vasculitis.

Table 1: Major clinical manifestations

Pulmonary	Restrictive>obstructive, lymphadenopathy, endobronchial/ parenchymal, interstitial lung disease, bronchiectasis, vasculitis, atelactasis. Laryngeal (hoarseness), sinusitis, nasal congestion, saddle nose.
Ocular	Uveitis, chorioretinitis, phalyctanular conjunctivitis, glaucoma, cataract, optic neuritis.
Dermal	Erythema nodosum, nodules, plaques, lupus pernio, alopecia, tattoo infiltration, ulceration.
Hepatic	Hepatomegaly, cirrhosis jaundice.
Nervous system	Cr. Nerves, meningitis, myelopathy, mono or polyneuritis.
Cardiac	Arrhythmia, heart blocks, cardiomyopathy, sudden death.
Salivary/lachrymal glands	Sicca syndrome
Hematological	Lymph nodes, Hypersplenism,
Musculoskeletal	Polyarthritis, polydactilitis, bone cysts.
Endocrine	High serum and urinary calcium, hypopitutarism, epididymitis.
Renal	Calculi, nephrocalcinosis, chronic renal failure

Extrapulmonary sarcoid

Extra pulmonary involvement may be observed without significant pulmonary disease. Constitutional symptoms which may be disabling are seen in up to 20% of cases. Severe nasal congestion and chronic sinusitis typically unresponsive to decongestant and inhaled steroids are observed in 5-10% of patients. Surgical intervention may result in destroyed nasal cartilage and "saddle nose" laryngeal sarcoid may present with hoarseness, stridor or acute respiratory failure. Such lesions are often associated with skin lesions.

Uveitis is the most common eye sign and may be the presenting manifestation associated with hilar lymphadenopathy. Other signs include chorioretinitis, phalyctanular conjunctivitis, chronic uveitis, anterior synechae, glaucoma and cataract. Chronic sarcoid of skin may manifest as plaques and subcutaneous nodules typically around hair lines, eyelids, ear nose mouth and extensor surface of arms and legs, besides alopecia, pruritis, and hypo or hyper pigmented patches.

Hepatic involvement is common but rarely the sole manifestation of the disease. Clinically this may resemble primary biliary cirrhosis but anti mitiochondrial antibodies are negative. Typically gamma-GT and alkaline phosphatase are raised. Liver biopsy may show nonspecific granulomas in all stages of development.

Myocarditis is apparent in 5% of cases but is a major cause of death in young patients. Clinically may present with arrhythmia, heart block, sudden death, congestive cardiomyopathy or angina. Endomyocardial biopsy is positive in up to 60% of the cases.

Neurological involvement is seen in <5% of patients, and include, most commonly cranial neuropathy (V, VI, VIII), which may be reversible with steroids, but can relapse[11]. Central nervous system (CNS) involvement manifest as mass lesion, meningitis, hydrocephalus, and hypopitutarism[12]. Spinal cord compression syndrome may present with paraplegia.

Salivary/parotid and lachrymal glands involvement may present with Sicca syndrome. Fever facial palsy and parotid enlargement may occur together (Hereford's syndrome) with bilateral hilar lymphadenopathy. Peripheral lymph-adenopathy is minimal and resolves spontaneously.

Splenic involvement is seen in 10-20% of cases often with hepatomegaly Occasionally enlargement is massive but hypersplenism is uncommon.

Bone infiltration is seen in 10-20% of cases, usually seen at autopsy. Arthralgias are frequent, but acute presentation with short lived polyarthritis and erythema nodosum is typical during early stage of disease. In chronic disease erosions are rare but punched out lesions with cystic changes and loss of trabeculae may be seen. Rarely polymyositis with raised creatine phosphokinase (CPK) may be observed.

Increased urinary and serum calcium results due to increased conversion of vitamin D2 to vitamin D3 by tissue macrophages[13] and Epitheloid cells at sites of granulomas. Nephrocalcinosis and nephrolithiasis with renal failure may result from asymptomatic hypercalcemia. Sarcoidosis has been seen in association with a variety of non-organ specific autoimmune diseases as well.

Dermal lesions not uncommonly can be a presenting feature. Ulcerative sarcoidosis effects mostly women, blacks and in young adulthood, involving lower limbs more often[14].

Clinical assessment

Clinical evaluation requires routine chest X-Ray, pulmonary function test (PFT), transfer factor (Tco), liver function tests (LFT), serum calcium, complete blood examination, urine examination, electrocardiograph and Tuberculin test, besides specific organ assessment.

Diagnosis

Diagnosis is established on the basis of compatible clinical presentation with chest X-Ray showing bilateral hilar lymphadenopathy para tracheal lymph nodes and noncaseating granulomas on biopsy (endobronchial/hepatic/dermal) after exclusion of mycobacterial infection. Clinical presentation may be highly suggestive and may not require biopsy for diagnostic confirmation. If easily accessible site for biopsy is not available blind fibreoptic bronchoscopic biopsy is helpful in up to 40-50% of cases. High CD4/CD8 cell count in bronchoalveolar lavage (BAL) may be present but shows low specificity and wide variability in levels. Increased Gallium 67 uptake is observed by hilar/ mediastinal lymph nodes, as well as by salivary and lachrymal glands (Panda sign). This test is not recommended for a diagnostic purpose.

Monitoring

Treatment decision is made on clinical grounds and specific organic function. Monitoring may be done through repeat serum angiotensin converting

enzyme (ACE) level ESR, serial chest x-Ray, pulmonary function tests, serum calcium, serum lysozyme concentration, CD4 count in bronchoalveolar lavage (BAL)., DTPA clearance and 67Ga scanning. Even induced sputum CD4/CD8 ratio and tumor necrosis factor (TNF) alpha level, correlates well with BAL levels[15]. Tumor necrosis factor (TNF) level may predict chronicity of the illness[16]. Gallium scan reflects lymphocyte differential count; and negative test does denote inactivity of the disease. Serum concentration of ionized calcium can be a useful index for the disease activity[17]. Conventional chest radiograph (Table-2) and high resolution CT (HRCT) findings though not specific enough for definitive diagnosis, can be used for activity evaluation[18].

Table 2: Radiographic grading

STAGE—0	Normal Chest X-Ray
STAGE—I	Bilateral Hilar Lymph Node (BHL)
STAGE—II	BHL + Parenchymal Infiltration
STAGE—III.	Parenchymal Infiltration only
STAGE—IV	Pulmonary Fibrosis
	(Stage-I &II require no treatment)

Prognosis[19]

Sarcoidosis has variable natural course; from an asymptomatic or self limiting to a progressive life threatening condition . Patients with Lofgren's syndrome, asymptomatic bilateral hilar lymph nodes (BHL), erythema nodosum have better prognosis. Patients with stage-II chest x-ray have relatively poor outcome. Asymptomatic extra-pulmonary disease has better prognosis than symptomatic disease. Blacks in USA have chronic and persistent disease.

Overall good prognostic signs include; erythema nodosum, preserved positive tuberculin test, age <40 years, females, absent extra pulmonary lesions.

Treatment[20,21]

In view of overall good prognosis, whenever possible symptomatic and localized therapy may be utilized. This include, analgesics/ antipyretics, local steroids for anterior ocular lesions and avoiding sunlight. Persistent and progressive symptoms are accepted indications for system treatment. Systemic steroids are indicated for persistent hypercalcuria, renal or hepatic dysfunction, uveitis not responding to topical therapy, pituitary disease, myopathy, enlarged spleen or hepersplenism or CNS and cardiac disease, Other indications include severe weight loss, fatigue and disfiguring skin lesions.

Corticosteroids[22,23,24]

Steroids are the mainstay of therapy. For patients with asymptomatic hilar or para tracheal LN, it is prudent to wait up to 6 months[25], as 30% of the cases will have spontaneous remission; rest require steroids for induction of remission. Initiating dose is generally 40 mg/day, which is reduced by 10 mg every fortnight, to the maintenance dose of 10-15 mg/day. The treatment should continue for 6-12 month before further tapering. For life threatening organ failure occasionally high dosages of pulse intravenous steroid therapy may be indicated. Only a small proportion of patients require lifelong maintenance steroids. When corticosteroid therapy is prolonged, complicated by unwanted side effects[26] or in these who become refractory to the therapy, other treatments have been used[27]. This include anti-malarial, immuno-suppressants, cytotoxic agents, anti-inflammatory substances and radiation, although their role in the treatment of sarcoidosis is unclear (Table-3).

Chloroquin: (alternate: Hydroxychloroquin with low toxicity but less effective)

These drugs are useful particularly in muco-cutaneous disease like, lupus pernio or nasal and laryngeal sarcoid. Chloroquin has shown promising results even in chronic pulmonary sarcoidosis[28].

Alternate drugs

Methotrexate (10-15 mg/ wk) is found to be safe, well tolerated and steroid sparing, particularly for severe skin or musculo-skeletal manifestation. Azathioprin (100 mg OD X 3-30 wk), chlorambucil, cxyphenbutazone, indomethacin, thalidomide,

Table 3: Second-line drugs with dosage schedule in sarcoidosis.

Drugs	Dose (mg)	Frequency	Duration (mo.)	Precautions
Hydroxychloruquine	200	Twice a day	3-6	Ocular toxicity
Methotrexate	10-15	Weekly	3-6	Hepatic toxicity
Azathioprine	150	Daily	3-6	Immuno-suppression
Cyclophosphamide	50	Daily	3	Immuno-suppresion
Chlorambucil	5	Daily	3	Immuno-suppression
Oxyphenobutazone	400	Daily	3-6	Peptic ulcer

tranilest and allopurinol has variable success. Experience with cyclosporin has proven disappointing.

Radiation

Whole body irradiation (total dose; 2-3,00 rads), or mega voltage radiotherapy has been found useful in brain, meningeal, posterior fossa granulomas and laryngeal sarcoidosis.

Heart-lung transplant

Heart lung transplant has some success when cardiomyopathy is present. Single lung or sequential transplant can be considered for patients with advanced diffuse fibrotic lung disease[29,30]. Transplanted lungs have also shown to develop subsequent granulomatous infiltration.

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