Sarcoidosis: A Multisystem Disease Demystified

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Introduction

Sarcoidosis is a multi-system granulomatous disease of unknown etiology, most commonly affecting adults and at times children. The disease characteristically causes bilateral hilar Lymphadenopathy and granulomatous, pulmonary, skin or ocular lesions. Sarcoidosis was first described in 1877 by the British surgeon dermatologist, Jonathan Hutchinson. Caesar Boeck of Oslo, Norway, fully described sarcoidosis in 1899, hence also known as Boecks sarcoidosis. **Venkatraman et al 1995** reported a case of papillary psoriasis; they discussed a 50 years old man who had non-tender purplish plaques on both hands and feet. Ten years later, the classic histological pattern of the disorder was described, and it was pointed out that the syndrome of sarcoidosis involved not only the skin but also the lymph nodes, the mucous involves and the lungs. At that time the disorder received its presently accepted name Sarcoidosis. Later sarcoidosis was more formally defined as a disease characterized by the presence of non-caseating epithelioid granulomas, proceeding either to resolution or to conversion into featureless hyaline connective tissue. According to the seventh International conference on Sarcoidosis and other granulomatous disorder, the findings required for a diagnosis of sarcoidosis include:

Clinico-radiographic evidence of multiple organ involvement, usually amplified bilateral hilar lymphadenopathy Pulmonary infiltration Pathological evidence of widespread non-caseating and non-infectious granulomas

Sex, Age and Race predilection:

Sarcoidosis affects individuals of any age, sex, race and geographic location. Young or middle-aged African American adults are more commonly affected. Peak incidence of the disease is seen in people aged 20-40 years and women appear to be slightly predisposed to sarcoidosis in pregnancy and lactation. When the disease develops in children it occurs in two distinct forms: -

- Early onset sarcoidosis – appears before the age of 4 years and is characterized by a triad of rash, uveitis and arthritis but no demonstrable pulmonary involvement
- Late onset sarcoidosis – appears in older children, who often develop a multi-system disease and exhibit hilar lymphadenopathy and pulmonary infiltration

Etiopathogenesis

Although the etiology of the disease is unknown, hypothetical causative agents include infectious organisms, environmental agents or auto-antigens. Two currently prevalent theories stress the role of: -

- Depression in cell-mediated immunity manifested by a decrease in circulation T cells and
- Mycobacterial infective agents in conjunction with genetic predisposition.

There has been some suggestion that sarcoidosis is a hereditary disease. Merchant et al found 75 cases of sarcoidosis affecting more than one member of 32 families. They suggest that a complex hereditary trait might be a factor in pathobiology of sarcoidosis. Immunodeficiency has been reported in association with sarcoidosis. This deficiency has been characterized by deficient T cell function with intact B cell function. Patients with sarcoidosis show a greater incidence of non-reactivity to inter dermal injections of common antigens such as Candida and purified protein derivatives as well. Sarcoidosis currently is considered a chronic inflammatory disease distinguished by hyperimmune reactions to an unspecified agent at the lesion sites. Continuous stimulation by the antigenic agents sustains the pathological process. A 2-stage theory of development for sarcoidosis has been derived: -

First stage is the pre-granulomatous inflammatory phase in which activated lymphocytes are the predominant cells of the lesion

Second stage is the granulomatous phase and is the active form of disease. The cellular immune response of sarcoidosis appears to be triggered by macrophages released cell mediators such as Interleukin 1 (IL-1), which stimulate the accumulation and proliferation of helper T lymphocytes. The helper T lymphocytes release mediators (Interferon- γ and lymphokines) that amplify the immune response by recruiting and activating mononuclear phagocytes.

Clinical features:

1. Respiratory involvement: The respiratory system is the most commonly targeted organ system in sarcoidosis. Approximately 90% of the patients with sarcoidosis have an abnormal chest radiograph during the course of their disease. In fact sarcoidosis is often incidentally diagnosed from routine chest radiographs. In the active state, the "classic picture" of a chest radiograph reveals bilateral hilar lymphadenopathy (Robert et al 1976). The most common symptoms associated with pulmonary adenopathy are dyspnea on exertion, fever, fatigue, dry cough and occasional wheezing. Pulmonary infiltration without demonstratable adenopathy may be associated with pulmonary fibrosis and are been in 14% of the affected patients (Batal et al 1999). Clinical evidence suggests that the lung is the first site of involvement. The process extends through the lymphatics to the hilar and mediastinal nodes. Progressive pulmonary sarcoidosis occurs in 20% of patients and results in pulmonary fibrosis and physiological abnormalities similar to other restrictive lung diseases (Saboor J 1992). The degree of pulmonary involvement has been classified into various stages with the prognosis becoming progressively worse as the stage advances (Hildebrand et al 1990).

Stage 0: - In stage 0 the chest roentgenogram is normal and only extra pulmonary involvement is noted. Approximately 8% of patients with sarcoidosis have a normal chest roentgenogram at the time of initial presentation. This stage may reflect a late phase of sarcoidosis in which the intra-thoracic manifestations originally present have cleared leaving only the extra thoracic lesions.

Stage I: - It is characterized by bilateral symmetric hilar lymph node enlargement without parenchymal changes.

- This is the earliest clinically detectable form of sarcoidosis
- Approximately 60% to 80% of those with stage I disease will undergo spontaneous resolution in 1 to 2 years.
- About 10% have clinically apparent extra thoracic manifestations including involvement of the eyes, lacrimal glands, salivary glands, skin or CNS.

Stage II: - A chest roentgenogram revealing hilar lymphadenopathy with a pulmonary infiltrate has been defined as stage II sarcoidosis. It occurs in 25% to 30% of the patients with about half of these persons showing radiographic resolution in 1 to 2 years. It is in this stage that steroid therapy is often initiated.

Stage III: - Roentgenographic clearing of intra-thoracic lymph nodes with persistence or progression of the pulmonary infiltrates characterizes stage III sarcoidosis

- Observed in 5% to 15% of patients
- Only 12% will have resolution
- Extra thoracic involvement, which may include chromic skin lesions, ocular lesions and occasionally bone cysts, accompanies stage III sarcoidosis more often than stage II and I.

2. Skin involvement: Granulomatous skin lesions have been reported in 10% to 30% of patients and are observed frequently among the American black population much more frequently in women (Hildebrand et al 1990). Skin lesions result from either granulomas (maculopapular, subcutaneous nodule, skin plaque and lupus pernio) or from a vasculitic response (erythema nodosum). Lupus pernio is a chronic condition characterized by indurated violaceous or red-purple lesions on the nose, checks, lips, ears and knees. Erythema nodosum is seen with acute and benign sarcoidosis and presents as bilateral tender red nodules in the skin or subcutaneous tissue (Gold et al 1976). Erythema nodosum is typically associated with bilateral hilar adenopathy as part of Lofgren's syndrome. Lofgren's syndrome (acute sarcoidosis) described in 1953, present as erythema nodosum, hilar adenopathy, fever, uveitis, and arthralgia. Prognosis is good with complete resolution of the symptoms in 90% of the cases (Batal et al 1999).

3. Eye involvement: Eye lesions are seen in approximately 25% of patients with sarcoidosis. Inflammation of the anterior uveal tract is the most common ocular lesion, but involvement of the conjunctiva, retina, and the lacrimal glands does occur. Keratoconjunctivitis sicca, with resultant dry eye occurs with lacrimal gland involvement. Patients usually complain of blurred vision tearing and photophobia (Batal et al 1999). The lesions are chronic and can progress to blindness if left untreated. Uveitis in association with parotid enlargement and cranial nerve palsies (especially of the seventh cranial nerve) has been described as Heerfordt's syndrome (uveoparotid fever) (Gold et al 1976).

4. Reticuloendothelial involvement: The Reticuloendothelial involvement is usually involved in the acute stage of disease. The liver is frequently affected and often becomes quite enlarged, but sever hepatic dysfunction is unusual. Elevation of serum alkaline phosphatase and 8-glutamythraus ferase is common. This is usually seen in 40% of patients with liver involvement. Chronic hepatitis and cirrhosis of the liver are rare presentations in liver sarcoidosis. Liver involvement can range from incidental tubercles, to granulomatous hepatitis, to post necrotic cirrhosis with portal hypertension and is heralded by elevation in bilirubin and alkaline phosphatase levels. Splenomegaly is seen in 5% to 10% of patents with sarcoidosis. Thrombocytopenia is occasionally present. Spleen involvement is associated with anemic thrombocytopenia, and leucopenia. In sarcoidosis, there is overproduction of vitamin D with resultant hypercalciuria and hypocalcaemia. This increase in the calcium load affects the kidneys and may cause nephrolithiasis and nephrocalcinosis with resultant renal insufficiency (Batal et al 1999).

5. Bone involvement: Bone changes are more common in chronic cases and are especially common in black persons with chronic skin involvement whose disease is more florid and progressive (Saboor J 1992). Osteoporosis cortical thinning and well-defined cysts that radiographically have an irregular lattice-like appearance have been described. Bony lesions are found in 5% of patients and are present as punched out radiolucencies. The phalanges, metacarpals and metatarsals are the most commonly affected bones; but the skull, nasal bones, ribs and vertebrae can be involved. Radiographs disclose intact periosteum, and sausage shaped swellings of interphalangeal joints. Arthritic symptoms may manifest acutely, as monoarthralgias or polyartharalgias but usually recede with no residual deformities (Batal et al 1999).

6. Cardiac involvement: About 5% to 10% of the patients have cardiac involvement with clinical evidence of cardiac dysfunction, including congestive heart failure, dysarhythmia, recurrent pericardial effusion, heart block and angina pectoris. Cardiac involvement (primary myocardial sarcoidosis) has been known to lead to paroxysmal arrythmias and sudden death.

7. Sarcoidosis in the oral cavity: Sarcoidosis rarely involves the oral cavity (Batal et al 1999). Lesions of the buccal mucosa and vestibule normally present as firm, asymptomatic, sub mucosal mass either attached to the underlying tissue or freely movable. They are non-tender, well-circumcised nodules or papules occasionally with superficial ulceration, appearing as brownish red or violaceous in colour (Hildebrand et al 1990). Cases involving the maxillofacial skeleton have been reported even less frequently. Thomas and co-workers reported sarcoidosis of the mandibular condyle and Cohen et al in 1981 documented a case of osseous involvement of maxilla and mandible. They reported that lesions when present have features such as early thinning and streaking of medullary margins, with progression to punched-out, lytic, cyst like areas. Corresponding clinical manifestations include tooth mobility, temporomandibular joint dysfunction and abnormal healing of extraction sites. Mandibular lesions have been reported most commonly in the premolar-molar region. Tongue lesions appear firm and indurated with corresponding tongue enlargement or as erosive papular lesions (Batal et al 1999). In case involving the floor of the mouth, ranula formation from the sublingual gland is the most common initial presentation. Although the incidence of asymptomatic Sarcoid ranula is low when present it may serve as a possible indicator of future development of symptomatic widespread sarcoidosis (Menderson et al 1991). Gingival involvement in sarcoidosis caused gingival enlargement with occasional ulceration (Batal et al 1999). Lip lesions present as either nonspecific swelling or submucosal nodules. Lesions involving the commissures and extending into the skin produce a chronic angular stomatitis that resembles persistent herpes labialis. Soft tissue involvement of the hard part and soft palate presents as multiple nodules. In cases involving the bony maxilla, the pre-maxilla is the most commonly involved region. On radiographic examination, lesions are diffuse radiolucencies with ill-defined borders and extend in some cases, to involve the nasal floor. All associated teeth are usually vital without root resorption. Progressive mobility of the teeth may occur with untreated lesions. Lymph node biopsy can be a useful diagnostic adjacent for intra oral lesion of sarcoidosis. Biopsy of an intra oral lesion or lymph node biopsy and Kveim testing are useful in establishing a diagnosis of sarcoidosis (Lindeboom et al 1999). The presence of non-caseating granulomas in salivary tissue is a specific feature of sarcoidosis. Involvement of the minor salivary glands and their biopsy as the initial diagnostic procedure for histologic confirmation of sarcoidosis has been widely reported. The salivary gland involvement may manifest itself in a variety of clinical patterns. The most common pattern is represented by major salivary gland swelling, with histologic involvement of the minor salivary glands. Xerostomia may be present and it is directly proportional to the extent of the granulomatous infiltration into the gland. Spontaneous regression of the swelling can be expected (Surattanout et al 2002). A second pattern of salivary gland involvement is characterized by the absence of clinical salivary gland swelling. Histologic examination of minor salivary gland biopsy specimens usually will reveal the presence of non-caseating granulomas in 38% of patients with known sarcoidosis, while labial salivary glands that have undergone a biopsy reveal granulomas in 58% of patients. A third manifestation of salivary involvement is uveoparotid fever, or Heerfordt's syndrome, which consists of a triad of symptom including bilateral parotid swelling, uveitis and cranial nerve involvement. This symptom complex rarely is seen in children. It is important for dentists to be aware that the first clinical sign of

sarcoidosis may be parotid or even submandibular salivary gland involvement, with parotid sialadenopathy a frequent finding in children. Salivary gland flow and enzyme content of amylase and kallikrein are significantly reduced in many patients during the active phase of disease (Batal et al 1999).

8. Nasal involvement: Involvement of the paranasal sinuses by sarcoidosis is rare. The nasal mucosa is involved in up to 20% of patients and usually presents as nasal stuffiness. Lindeboom et al in 1999 reported a case of sarcoidosis with sinusitis as its first indication. In patients with sarcoidosis, nasal involvement may be the first symptom of the disease. Symptoms in patients with sarcoidosis usually comprise nasal obstruction, epistaxis, nasal pain, nasal crusting, or discharge, epiphora, anosuria or lyposuria and dyspnea. The inferior turbinate and the septum are most commonly involved. The nasal obstruction caused by polypoid hypertrophy can be aggravated when stagnation and crusting lead to suppuration, discharge and epistaxis. Sarcoidosis can also cause destruction of the osseous wall of the Para nasal sinuses and the nasal septum.

9. Nerve involvement: The facial nerve is the most commonly involve cranial nerve in sarcoidosis either alone or in association with Heerfordt's syndrome, with resultant facial palsy (Batal et al 1999). Involvement of the inferior alveolar nerve has been reported with parasthesia of the lip (Saboor J 1992). Cranial nerve palsy may result from direct involvement of nerve sheaths. If the pituitary gland is involved diabetes insipidus may result while, with cerebral cortex involvement, seizures may ensue (DeLuke et al 1985).

Histological features: Sarcoidosis is histologically defined as "a disease characterized by the presence of non-caseating epithelioid-cell granulomas, proceeding either to resolution or to conversion into featureless hyaline connective tissue" (Cohen et al 1981). Histopathologically the non-caseating epithelioid granuloma is the most distinguishing feature of sarcoidosis, but such findings are not pathognomonic. The granuloma is composed of epithelioid histiocytic cells, scattered giant cells of the Langhan's type and lymphocytes (Gold et al 1977). The giant cells are monocyte-derived and the Langhan's type having horseshoe shaped arrangement of nuclei. Giant cells may or may not have cytoplasmic inclusions (DeLuke et al 1985). Ackerman et al 1995 mention that the diagnosis of sarcoidosis must be one of exclusion, since non caseating granulomatous inflammation can occur in tuberculosis and other mycobacterial infections fungal infection, leprosy, syphilis, Crohn's disease, Hodgkin's disease and others. Necrosis is generally absent but central areas of fibrinoid necrosis are usually found with the deposition of eosinophilic fibrillar material (DeLuke et al 1985). Various nonspecific giant cell inclusions are also commonly found. These include Schaumann bodies and asteroid bodies.

- Schaumann bodies (conchoids bodies), which are lamellar structure, thought to be protein impregnated by calcium carbonate
- Asteroid bodies are stellate inclusions and probably composed of phospholipids (**Cohen et al 1981**).

These structures however occur in other types of granulomas and are therefore not indicative of Sarcoid.

Diagnosis:

There is no single laboratory test or clinical pathological feature that is absolutely diagnostic of sarcoidosis (Saboor J 1992). A definitive diagnosis of sarcoidosis is best achieved by integrating clinical data with the presence of non-caseating granulomas (Surattanout et al 2002). Confirmation of a clinical diagnosis of sarcoidosis can be established on the cumulative basis of the patient's medical history, clinical examination results, chest radiographic findings, elevated serum ACE levels and the results of microscopic examination of a labial gland biopsy specimen with the use of special stains. Hematological findings are not diagnostic for sarcoidosis but can be used to monitor disease activity. Complete blood count is usually of no diagnostic value and the erythrocyte sedimentation rate is only slightly elevated (67%) (Batal et al 1999). Blood picture shows hemolytic anemia, leukopenia, thrombocytopenia and eosinophilia (Cohen et al 1981). Patients may often have hyperglobulinemia or increased intestinal calcium absorption resulting in hypercalciuria because of increased production of 1, 25-dihydroxy, vitamin D in the Sarcoid nodules (Batal et al 1999). An additional laboratory test that has been described in recent yeas is the serum angiotensin converting enzyme (ACE) assay. The macrophages and epithelioid cells in the granuloma produce angiotensin-converting enzyme. Radiochemical assay of ACE can be helpful in collaborating a diagnosis, assessing the likely hood of spontaneous remission or evaluating the clinical course of the disease (DeLuke et al 1985). A significant elevation is generally defined as a level greater than 57 units per millimeter. Up to 80% of the patients with sarcoidosis will show on elevation of this enzyme. The test is not entirely specific, although it is highly suggestive when considered in association with hilar lymphadenopathy. Other conditions that may cause an elevated ACE include Gaucher's disease, leprosy, and certain malignancies (Hildebrand et al 1990). The Kveim Siltzbach reaction may also play a role in diagnosis. This test is performed by injecting a sterilized suspension of human Sarcoid tissue intra-cutaneously. A nodular lesion with epithelioid tubercles will develop 4 to 6 weeks after injection in 50% to 80% of Sarcoid patients. False positive results with the Kveim reaction may occur in 2% to 5% of patients, with other granulomatous or collagen vascular disease, and false negative results may be present in mild forms of the disease or when corticosteroid therapy is being given (Steinberg et al 1994). Liver involvement occurs in about 75% of cases and is associated with mild hyperbilirubinemia and a significant elevation of the level of alkaline phosphatase (Cohen et al 1981). Hypocalcaemia is an extremely variable finding, and is present in form 13% to 63% of all cases. When present, hypocalcaemia can lead to nephrocalcinosis, and subsequent renal failure. Bronchoalveolar lavage can be diagnostically helpful and typically demonstrates an increased proportion of activated helper T lymphocytes in affected patients (Batal et al 1999). Gallium 67 may be useful in detecting unsuspected organ involvement by sarcoidosis and determining disease activity (Steinberg et al 1994). High-resolution computed tomography has been shown to be superior to plain film radiography in diagnosing early fibrosis of the lungs and may have diagnostic advantages over the standard chest radiograph (Batal et al 1999). Immunologic features include a depression of delayed type hypersensitivity reflected by T-cell anergy, suggesting impaired cell mediated immunity and elevated or abnormal immunoglobulin (IgG, IgA, IgM) levels. Hypercalciuria may be present with or without hypercalcemia (Hildebrand et al 1990).

In case of salivary gland involvement, stimulated salivary volume method could be of a diagnostic aid. Done using a modified Carlsen-Crittenden collector, to measure stimulated salivary volume from each parotid gland individually (Normal value of salivary production is 0.5% to 1.0 ml /minute). Further more the increase in the viscosity of saliva indicates the presence of an inflammatory process. The salivary chemistry in sarcoidosis involvement of salivary glands would show significant elevations of electrolyte and protein levels.

Treatment:

There are a few guidelines for the initiation of therapy for sarcoidosis. Establishing standardized guidelines for is complicated by:

- Diverse manifestation of the disease
- Frequent cases of spontaneous recovery without treatment and
- Significant side effect associated with existing treatment options

An observation period of 3 to 12 month is usually recommended to determine the general course of the disease (**Saboor J 1992**). There is no standard treatment for patients with stage II disease or I since spontaneous remission in two or three months is common. Patients with stage III Sarcoid have few spontaneous remissions and will most likely have decreased pulmonary function due to development of chronic pulmonary fibrosis. These patients require medical treatment (**Steinberg et al 1994**). The therapy of choice for sarcoidosis is corticosteroids. Corticosteroids can control the regulation of various mediators involved in the pathogenesis of sarcoidosis (1L-2, interferon-γ, tumor necrosis factor and IL-1). The current regimen for treatment is the daily use of 30 to 40 mg of prednisolone for 8 to 12 weeks, followed by gradual tapering of the dose to 10 to 20 mg every other day for 6 to 12 month until an optimal minimal dose is established. This dosing pattern is repeated if the disease becomes active again. Corticosteroid treatment has been shown to improve function of the involved organs during the treatment phase but not difference was noted in the long-term outcomes

of the disease (**Batal et al 1999**). Corticosteroid therapy in stage II patients or I only accelerates the disappearance of sarcoidosis symptoms and is only indicated if the disease persists or is worsening (**Steinberg et al 1994**). Steroids will usually present the progression of the disease but will not reverse fibrotic pulmonary changes. Treatment typically last for 6 to 8 months, but lifelong therapy may be necessary in some cases (**DeLuke et al 1985**). For patients with chronic or refractory disease, cytotoxic drugs such as methotrexate, azathioprine, chlorambucil and cyclophosphamide have been used to avoid the complications of steroids. Among these cytotoxic drugs, methotrexate has given the best results. Methotrexate is also used for the treatment of musculoskeletal sarcoidosis because it is often refractory to treatment with steroids (**Batal et al 1999**). Mc Cafrey and Mc Donald advocated treatment of sarcoidosis of the sinuses by application of topical corticosteroids. The discomfort of nasal crusting can be relieved with frequent nasal irrigation.

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