Ocular Sarcoidosis

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Sarcoidosis

Sarcoidosis is a multisystem granulomatous disease which was first described by Jonathan Hutchinson in 1878. Its clinical manifestations and course can be variable in different ethnic groups. The organs affected more often are the lungs, skin and eyes.

The frequency of ocular involvement ranges from 26% to 50%. The characteristics of ocular involvement are (1) when present, is seen generally early in the course of the disease (2) may co-exist with asymptomatic systemic disease and (3) can precede systemic involvement by several years. Most patients present between the ages of 20 to 40 years; however, children and the elderly can be affected. Cases of familial sarcoidosis, including monozygotic twins, and husband-wife pairs have also been reported.

Diagnosis relies on demonstration of non caseating granuloma by tissue biopsy. In cases of suspected sarcoidosis where no affected tissue amenable to biopsy is identifiable, supportive evidence of the diagnosis can be obtained through non-invasive investigations including measurement of serum angiotensin converting enzyme (ACE) and lysozyme, chest x-ray, chest computerized tomography (C-T), gallium scintillography, pulmonary function tests, bronchoalveolar lavage, and measurement of serum and urinary calcium.

Ocular manifestations

Anterior segment

Conjunctival involvement has been reported in 6.9%-70% of patients with ocular sarcoidosis (**Figure 1**). Sarcoidosis granulomas are described as solitary, yellow "millet-seed" nodules. Anterior uveitis occurs in 22%-70% of patients with ocular sarcoidosis, and is usually granulomatous and chronic. Iris nodules have been reported in up to 12.5% of patients with sarcoidosis associated uveitis. Exacerbations of granulomatous uveitis are often associated with an appearance of fresh iris or fundus nodules. Posterior synechiae, cataract and glaucoma are common complications. Corneal band keratopathy develops in a few patientsand is usually associated with hypercalcemia.

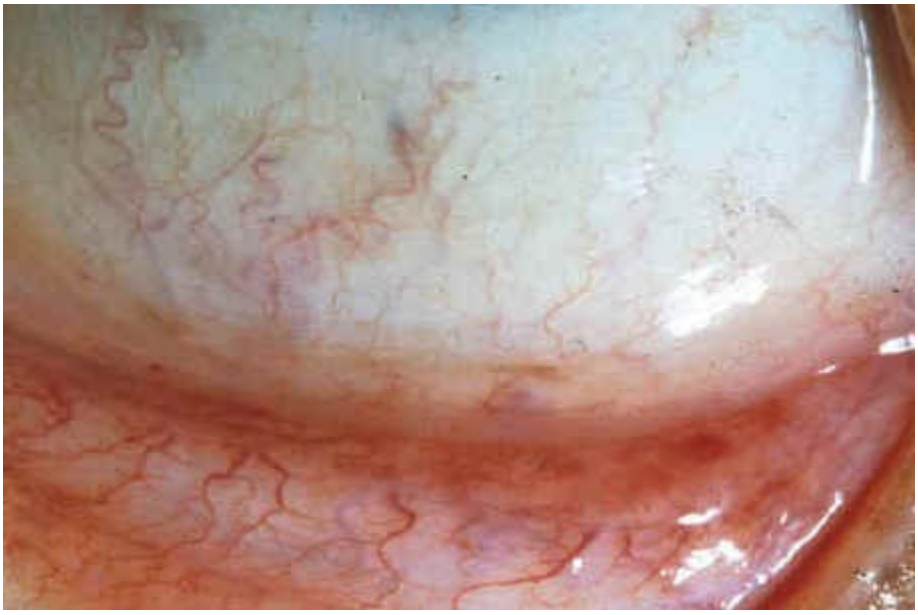


Figure 1. Conjunctival nodules in a patient with sarcoidosis.

Posterior segment

The most common manifestations at the posterior segment are vitritis, intermediate uveitis, panuveitis, posterior uveitis, retinal vasculitis and optic nerve involvement. Other manifestations include choroidal nodules and exudative

retinal detachment. Clinical and/or angiographic cystoid macular edema (CME) has been reported in 19%-72% of patients. Overall, patients with chronic posterior uveitis and panuveitis have significantly more complications than do patients with anterior uveitis. "Candle wax drippings" and "punched-out" lesions can be seen in patients with uveitis secondary to sarcoidosis (**Figure 2**).

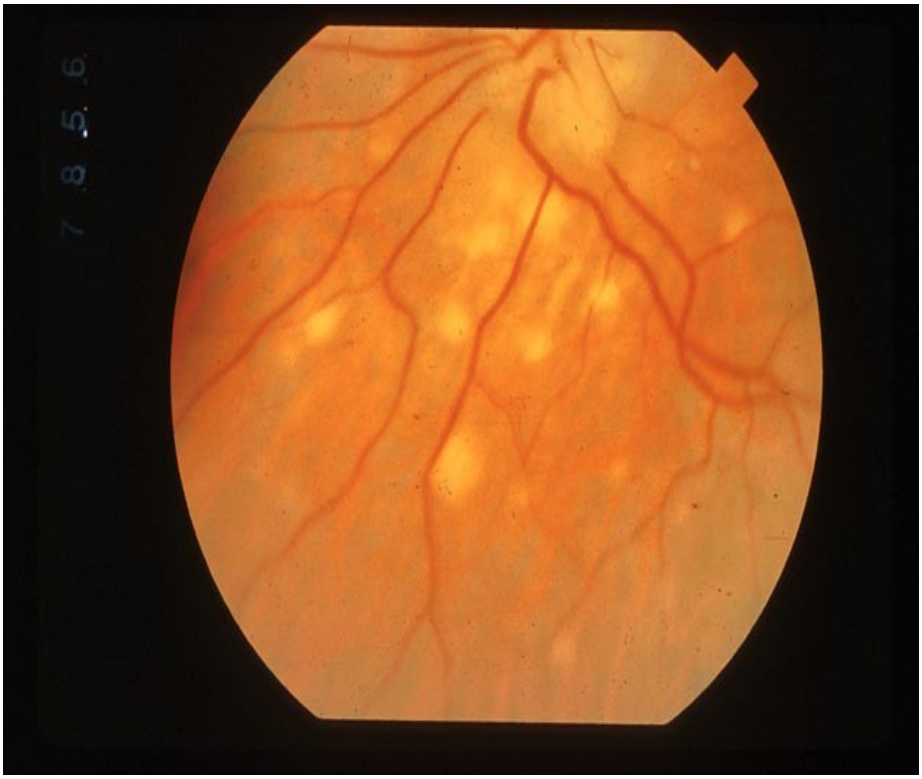


Figure 2. Punched-out choroidoretinal lesions in a patient with sarcoidosis.

Severe retinal vasculitis and ischemic retinopathy with neovascularization, requiring scatter photocoagulation has been described in some patients. Other less frequent complications include peripapillary and subfoveal choroidal neovascularization, posterior scleritis with annular ciliochoroidal detachment causing angle closure glaucoma, and central retinal vein occlusion leading to a painful blind eye from neovascular glaucoma.

Orbit

Although sarcoid granulomas have been described in most areas inside the orbit, the lacrimal gland appears to be the organ most commonly affected. The frequency of lacrimal gland involvement varies from 7% to 69%. The nasolacrimal drainage system can also become involved in patients with sarcoidosis. The patients usually present with epiphora and nasal stuffiness. Extraocular muscle involvement can occur and presents with diplopia or painful external ophthalmoplegia.

Sarcoidosis in childhood

Early onset or pre-school sarcoidosis seen in children is relatively rare. The classic triad of symptoms consists of skin, eye and joint lesions; pulmonary involvement is rare, at least initially. It can be easily misdiagnosed as juvenile rheumatoid arthritis, as the latter also presents with symptoms from the joints and eyes.

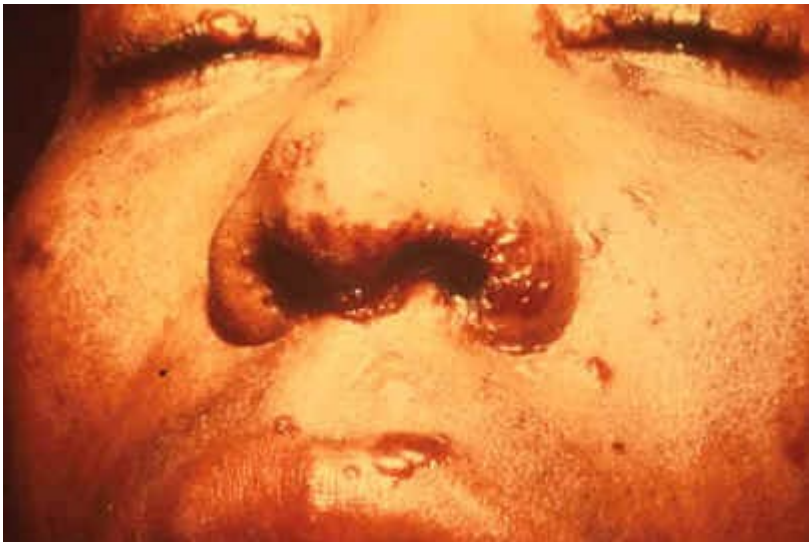
Extraocular involvement

The lung is the most frequently affected organ in patients with sarcoidosis. Histologically the lesions are distributed primarily along the lymphatics around bronchi and blood vessels, although alveolar lesions are also seen. The relative frequency of granulomas in the bronchial submucosa accounts for the high diagnostic yield of bronchoscopic biopsies. Lymph nodes are involved in almost all cases, especially the hilar and mediastinal ones. The majority of patients are asymptomatic, while others may complain about cough or shortness of breath.

The spleen is enlarged in only 18% of cases, although microscopical evidence of sarcoid granulomas in spleen is present in three-quarters of the cases. The liver is affected less often than is the spleen, but a finding of elevated liver enzymes in a sarcoidosis suspect may prompt percutaneous liver biopsy in the search for histopathologic

confirmation of the suspected diagnosis. Renal insufficiency has been reported in patients with histologically proven sarcoidosis of the kidneys and has been attributed to hypercalcemia and interstitial granulomatous nephritis. X-ray abnormalities of the bones can be identified in about one-fifth of patients. The radiologically visible lesions are usually seen in the phalangeal bones of the hands and feet, creating small circumscribed areas of bone resorption within the marrow cavity.

Skin lesions are found in 9%-37% of the patients. They may be specific, showing histologically non caseating granulomas, or non-specific, e.g. erythema nodosum. The specific skin lesions include lupus pernio, infiltrated plaques, maculopapular eruptions, subcutaneous nodules and infiltration of old scars (Figures 3 & 4).



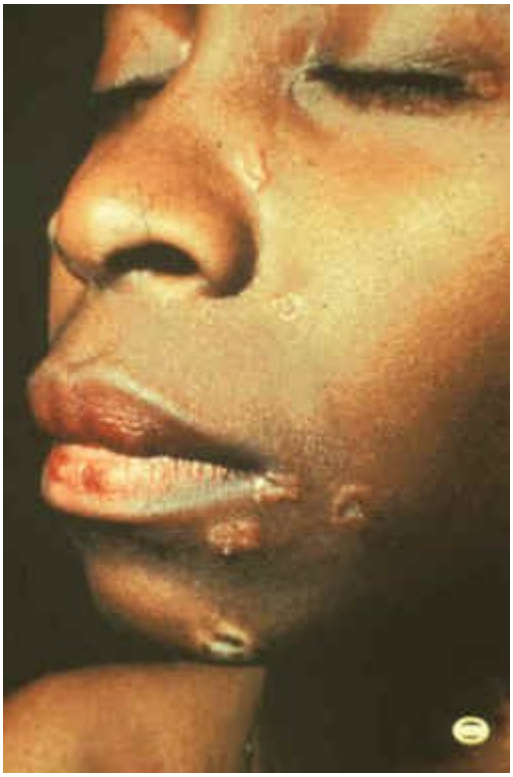


Figure 3 & 4. Skin manifestations in patients with sarcoidosis.

Histology

The hallmark of sarcoidosis is a non necrotizing granuloma. The center of the granuloma consists of histiocytes, epithelioid cells, and multinucleated giant cells which are surrounded by lymphocytes, plasma cells, and fibroblasts (**Figure 5**). Gross necrosis is not a feature of sarcoidosis, and suggests alternative diagnoses (e.g. tuberculosis,

fungal infection, vasculitis, etc). The epithelioid cells are transformed bone marrow monocytes and have marked secretory activity which includes over 40 different cytokines and other mediators. Among the enzymes and other chemicals secreted by granulomas are ACE, lysozyme, glucuroonidase, collagenase, and calcitriol.

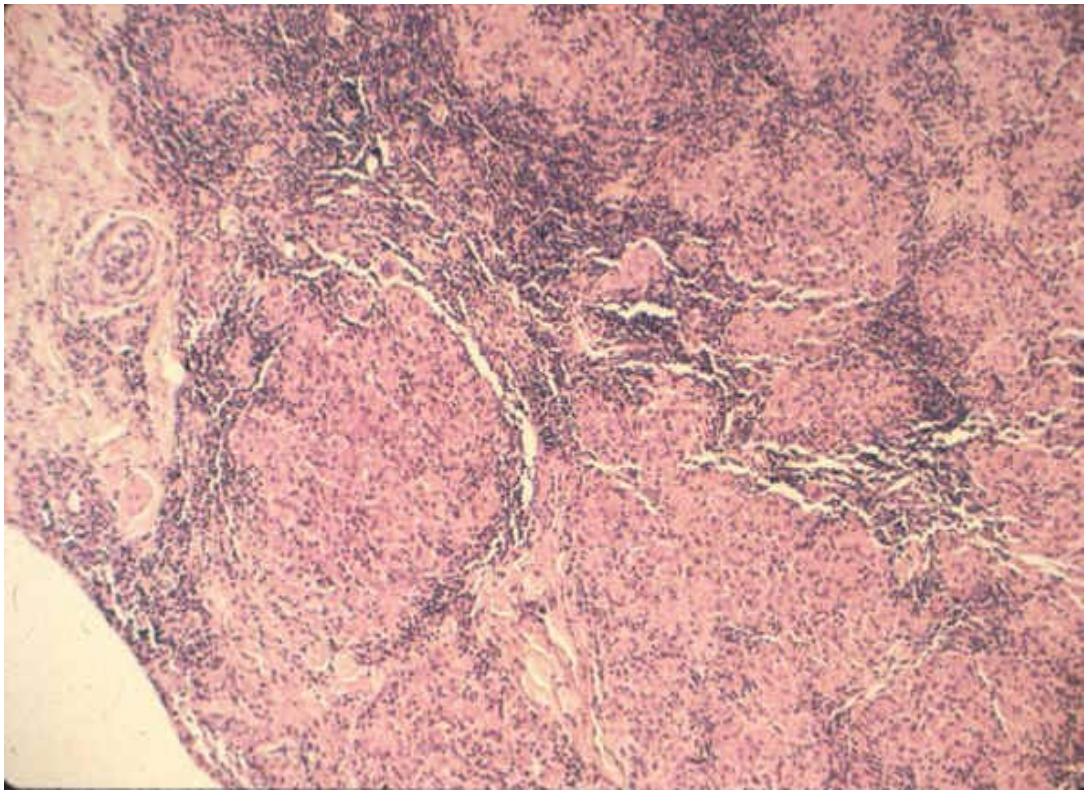


Figure 5. Granulomas consisting of histiocytes, epithelioid cells, and multinucleated giant cells.

Kveim test

In 1941, Kveim reported the use of a suspension derived from the spleen of a patient with sarcoidosis that, when injected intracutaneously into patients with biopsy proven sarcoidosis, yielded a cutaneous papule containing non caseating epithelioid granulomas. Four to six weeks following subcutaneous injection of the Kveim reagent, the typical lesion presents as a red or brownish raised papule ranging from a few millimeters up to 1.5 centimeters in diameter. Histopathologic analysis of the biopsied lesion reveals a granuloma composed of epithelioid cells, occasional Langhans cells and scattered lymphocytes at its center with a surrounding cuff of mononuclear cells, primarily lymphocytes.

Cutaneous anergy

In 1916, Boeck first described cutaneous anergy to tuberculin in patients with sarcoidosis. It was later on realized that this phenomenon was not limited to tuberculin alone, but that anergy to a variety of other skin tests-antigens such was also typical. In 1994, Kataria and Holter proposed a mechanism for the cutaneous anergy seen in sarcoidosis. At sites of granulomatous inflammation, there is a predominance of helper T lymphocytes, which proliferate and secrete large amounts of lymphokines, including interleukin (IL)-2, monocyte chemotactic factor (MCF) and migration inhibition factor (MIF). These lymphokines induce and amplify the immune response by enhancing T-lymphocyte proliferation as well as recruiting and retaining monocytes from the circulation. The lymphokines and monokines produced at sites of granulomatous inflammation have their highest concentration locally. Nevertheless, the protein molecules diffuse into blood, establishing a concentration gradient between the granulomatous inflammatory site and the remote site of the delayed type hypersensitivity (DTH) skin test. As a result, the traffic of T-helper lymphocytes and monocytes is preferentially directed towards site of granuloma formation. That leads to a preponderance of suppressor cells in the peripheral blood and competitively depletes the T-helper cells and monocytes available to sites of DTH.

Etiology and pathogenesis

The processes involved in the pathogenesis of sarcoidosis in the lungs include accumulation of CD_4+ lymphocytes at the affected site. The cytokines and factors secreted by these cells account for the influx of monocytes, alveolitis,

and non caseating granuloma formation in the lung and for the resulting progressive fibrosis, all characteristic features of pulmonary sarcoidosis. Sarcoidosis is characterized by "compartmentalization" of the T cells, such that the relative proportion of CD_4+ T cells in blood is reduced (e.g. CD_4/CD_8=0.8), while the reverse relation is observed in affected tissue (e.g. CD_4/CD_8=1.8 in lung). The CD_4+ cells in the involved organs are "activated" and thus are releasing IL-2 and other mediators, while the CD_4+ cells in other sites, such as blood, are quiescent.

In 1992, Holter et al demonstrated a Kveim-like granulomagenic activity in nonviable autologous BAL cells (NABC) recovered soon after symptomatic onset or relapse of sarcoidosis but not in patients with chronic stable sarcoidosis.The same group of investigators demonstrated a Kveim-like granolomagenic activity of peripheral blood monocytes, the progenitors of the alveolar macrophage. These findings suggest that the circulating monocyte is already primed with the granulomagenic factor before differentiation into alveolar macrophage. A monocyte source of the factor explains the multisystem distribution of granulomas in sarcoidosis.

Chest radiology

Sulavik et al suggested the following roentgen staging of sarcoidosis: 0= normal chest radiograph; 1= bilateral symmetrical hilar lymphadenopathy (BSHL) only; 2= BSHL with bilateral, symmetrical lung infiltration (**Figure 6**); 3= bilateral symmetrical lung infiltration only; 4a= BSHL with bilateral symmetrical lung infiltration indicative of pulmonary fibrosis (BSIF); 4b= BSIF only.

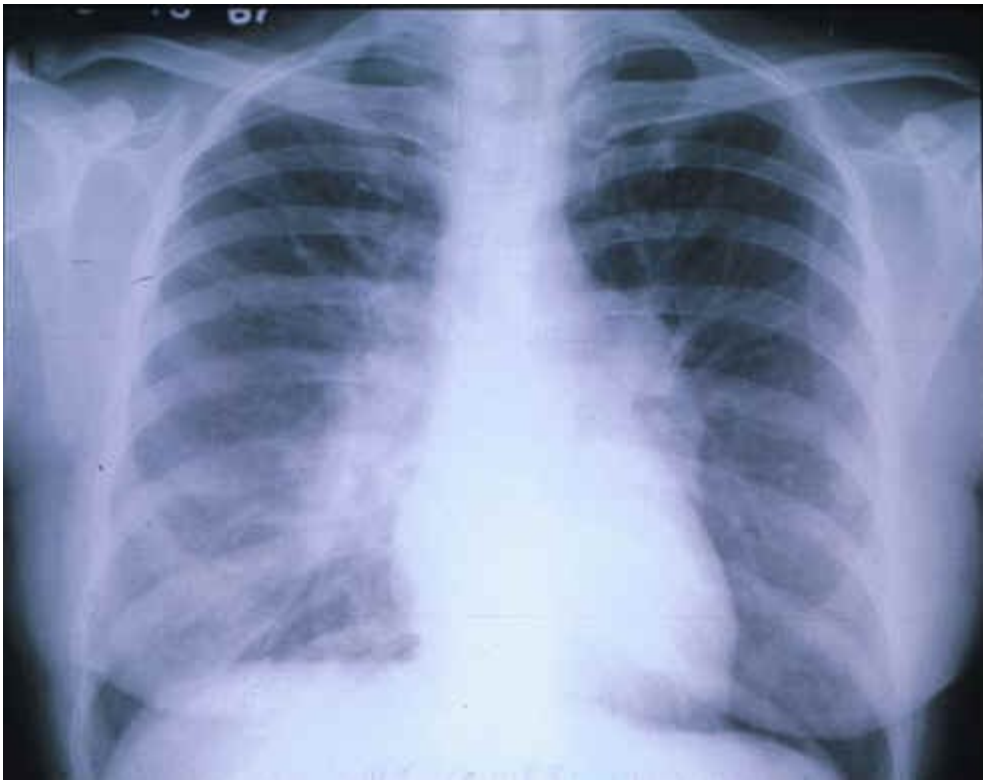


Figure 6. Bilateral symmetrical hilar lymphadenopathy and lung infiltration.

Gallium (^{67}GA) scan

The combined abnormal bilateral symmetrical ^{67}GA uptake of the lacrimal and parotid glands (with or without submandibular gland ^{67}GA uptake) is called the "panda" pattern (Figure 7). The presence and pattern of ^{67}GA uptake in both (1) the parahilar and infrahilar bronchopulmonary lymph nodes and (2) the right paratracheal (azygous) mediastinal lymph nodes is called the "lambda" image after its resemblance with the Greek letter l.

Pulmonary uptake of ^{67}GA is sensitive but not specific in the diagnosis of pulmonary sarcoidosis as it can occur in a wide variety of other inflammatory and neoplastic diseases.Abnormal ^{67}GA uptake in salivary and lacrimal glands may also occur in Sjögren's syndrome, tuberculosis and after radiation therapy.

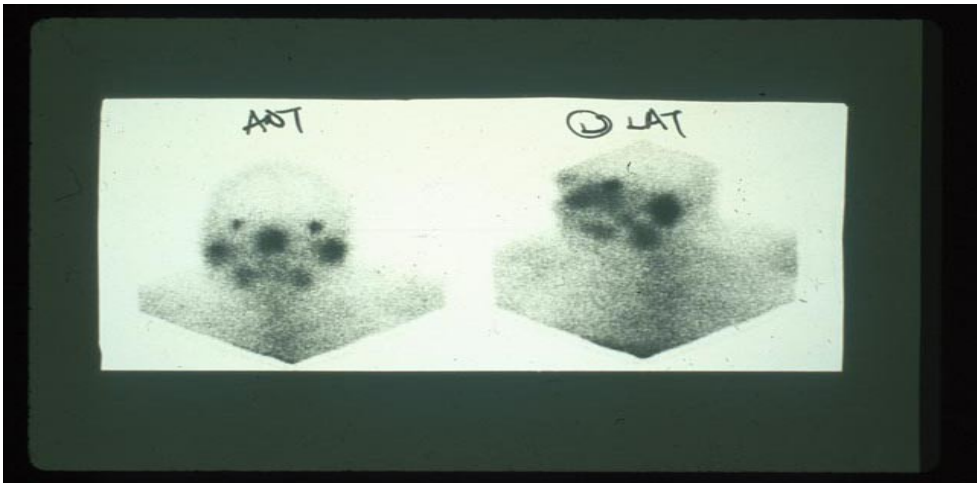


Figure 7. Bilateral symmetrical gallium uptake by the lacrimal, parotid, and submandibular glands (Panda sign).

Angiotensin converting enzyme (ACE)

ACE is normally present in the vascular endothelium of many organs (lung, kidney, small intestine, uterus, prostate, thyroid, testes, adrenals) and in macrophages. The latter source accounts for elevated ACE levels in patients with sarcoidosis. The induction of ACE synthesis in epithelioid cells and macrophages is caused by a soluble ACE-inducing factor (AIF). ACE is elevated in 60-90% of patients with active sarcoidosis. A normal serum ACE does not exclude the diagnosis, especially if the disease is in its early stages, localized to a small area (e.g. the eye), and therefore with a small epithelioid cell "barden". False low values are also measured in patients taking ACE inhibitors or in patients with endothelial abnormalities, such as deep vein thrombosis, and in patients who have had chemotherapy or radiation. Treatment with systemic steroids or other immunosupressive agents can also affect ACE levels with values normalizing with adequate control of intraocular inflammation. Other disorders associated with elevated serum ACE include Gaucher's disease, leprosy, chronic pulmonary disease, rheumatoid arthritis, spondylitis, primary biliary cirrhosis, tuberculosis, histoplasmosis, histiocytic medullary fibrosis, hyperthyroidism and diabetes mellitus.

Pulmonary function tests

Pulmonary function tests are useful in the initial diagnosis and follow up of patients with sarcoidosis. Their sensitivity in disease with and without roentgen evidence of parenchymal involvement has been reported as 70% and 40% respectively. The most common abnormalities seen early in the course of the disease are a post exercise increase in the alveolar-arterial oxygen gradient and diffusing capacity and a reduction in lung compliance.

Bronchoalveolar lavage (BAL)- Transbronchial lung biopsy (TBLB)

The earliest pathologic finding in patients with sarcoidosis is a mononuclear alveolitis composed of increased CD_4+ lymphocytes (with an increased CD_4/CD_8 ratio), monocyte-macrophages, and rare B lymphocytes. Tissue for biopsy from the bronchial mucosa or the adjacent lung is obtained through a fibreoptic bronchoscope. Non caseating granulomas have been reported in 54-88% of patients who underwent TBLB.The rate of positive findings by TBLB is higher in patients with radiologic evidence of pulmonary infiltration, and is approximately 60% among patients with hilar lymphadenopathy whose chest radiographs show normal lung parenchyme.

Hypercalcemia

Hypercalcemia has been reported in 10-15% of patients with sarcoidosis and is related to increased serum concentrations of 1,25-dihydroxy-vitamin D_3 (calcitriol). Calcitriol is produced at sites of active disease by alveolar macrophages and possibly T lymphocytes. Elevated serum levels of calcitriol in hepercalcemic patients with sarcoidosis lead to increased absorption of calcium and phosphate from the gastrointestinal tract which leads to hypercalcemia and hypercalciuria.

Lysozyme

Lysozyme is an enzyme normally secreted by monocytes and polymorphonuclear leukocytes. Several reports have shown that the levels of serum lysozyme are raised in patients with sarcoidosis and may be related to disease activity. Raised lysozyme levels have been reported in parallel to raised serum ACE levels. It is thought that the epithelioid cell of the sarcoid granuloma is the source for both lysozyme and ACE.

Conjunctival biopsy

The positive yield of conjunctival biopsy ranges from 14% to 40.4 %. The lower fornix is the most preferred site and topical anaesthesia is sufficient. A higher positive yield has been reported in patients with follicles, those with ocular abnormality consistent with sarcoidosis, those with pulmonary infiltrates and those with histologically confirmed non ocular sarcoidosis. Furthermore, examination of multiple sections of each biopsy is also recommended as granulomas may be present in limited numbers which may be missed if the number of sections is not adequate.

TREATMENT

The treatment of ocular sarcoidosis depends on the type of involvement. Mild anterior uveitis is treated by topical steroids and cycloplegics. Systemic steroids are indicated in anterior uveitis not responding to topical steroids, and in patients with posterior uveitis, neovascularization, or orbital disease with visual symptoms or optic nerve compromise. Patients who are refractory to steroids may respond to the addition of oral non steroidal anti-inflammatory drugs. If inflammation persists, chemotherapy (azathioprine, cyclosporin, methotrexate) may be required. Secondary glaucoma not responding to medical treatment has been treated by trabeculectomy and cryoablative therapy.Retinal neovascularization with evidence of ischemia on angiography responds well to panretinal photocoagulation.

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