International Journal of Advanced Research and Review

www.ijarr.in

SARCOIDOSIS: AN UPDATE

Qadir Fatima[*], Suman Kapuriy[*]a, Mukesh Kumar[**], L.A.Gauri[**], Harshal Pankaj[**]

[*]Department Of Pathology, S.P. Medical College, Bikaner
[**]Department Of Medicine, S.P. Medical College, Bikaner
Corresponding Author: Dr. L.A.Gauri, 4-D-116 Gyan Marg, Jnv Colony, Bikaner – 334003, Rajasthan, India, Email: drliyakatgauri@rediffmail.com

ABSTRACT

Sarcoidosis is a multisystemic disorder of unknown cause characterized by the formation of immune granulomas in involved organs. It is an ubiquitous disease with incidence (varying according to age, sex, race and geographic origin) estimated at around 16.5/100,000 in men and 19/100,000 in women. The lung and the lymphatic system are predominantly affected but virtually every organ may be involved. Other severe manifestations result from cardiac, neurological, ocular, kidney or laryngeal localizations. Abnormal metabolism of vitamin D3 within granulomatous lesions and hypercalcemia are possible. Chest radiography is abnormal in about 90% of cases and shows lymphadenopathy and/or pulmonary infiltrates (without or with fibrosis).The etiology remains unknown but the prevailing hypothesis is that various unidentified, likely poorly degradable antigens of either infectious or environmental origin could trigger an exaggerated immune reaction in genetically susceptible hosts. Diagnosis relies on compatible clinical and radiographic manifestations, evidence of non-caseating granulomas obtained by biopsy through tracheobronchial endoscopy or at other sites, and exclusion of all other granulomatous diseases. Mortality is estimated at between 0.5–5%. In most benign cases (spontaneous resolution within 24–36 months), no treatment is required but a regular follow-up until recovery is necessary. In more serious cases, a medical treatment has to be prescribed either initially or at some point during follow-up according to clinical manifestations and their evolution.

INTRODUCTION

Sarcoidosis is a disease involving abnormal collections of inflammatory cells that form lumps known as granulomas. The disease usually begins in the lungs, skin, or lymph nodes. Less commonly affected are the eyes, liver, heart, and brain. Any organ, however, can be affected. The signs and symptoms depend on the organ involved. When it affects the lungs there may be wheezing, cough, dyspnoea, or chest pain.

ETIOLOGY AND PATHOGENESIS

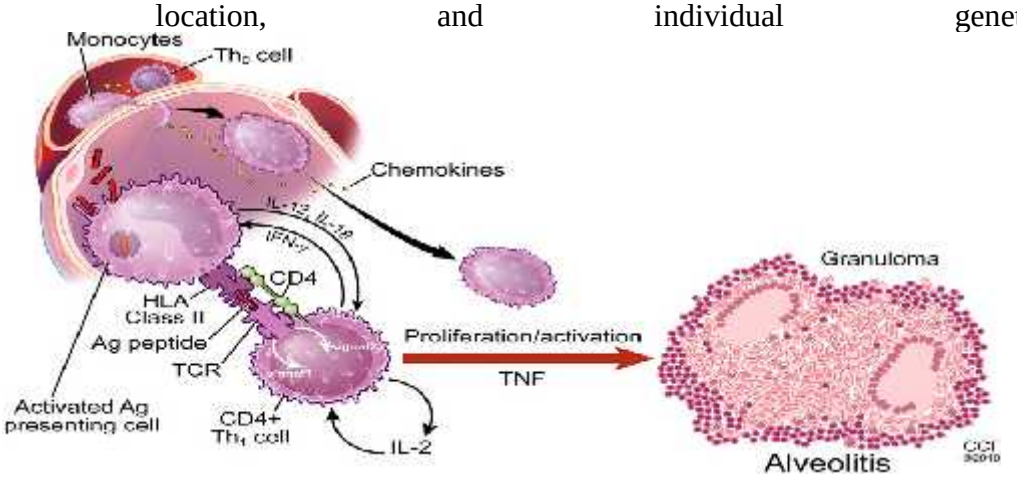
The immunopathogenesis of sarcoidosis is not completely understood, but there has been tremendous progress in the past decade. Most evidence suggests that the development of the disease is similar to other granulomatous diseases of known cause, such as chronic beryllium disease. That is, some antigen(s) enter the host and are phagocytosed by antigen-presenting cells (APCs), predominantly macrophages or dendritic cells. The APCs process the antigen and subsequently present it via human leukocyte antigen (HLA) class II molecules to a restricted set of T-cell receptors on naive T lymphocytes, primarily of the $CD4^+$ class. Induction of the immune response depends on intact cell-mediated immunity, as evidenced

by the phenomenon of reactivation sarcoidosis coinciding with immune reconstitution during treatment for HIV[2]. The immune reaction begets polarization of the T lymphocytes to a Th1 phenotype, followed by cellular recruitment, proliferation, and differentiation leading to formation of the sarcoid granuloma. A Panoply of cytokines and chemokines has been reported in association with sarcoidosis, but the relative importance of most of them is unclear.

The pathogenesis of sarcoidosis seems to involve the interplay of antigen, HLA class II molecules, and T-cell receptors[3]. If this scenario is correct, the pathophysiology of sarcoidosis depends on genetics that determine specific HLA polymorphisms, exposures in the form of putative antigens, and T-cell responses that may be genetically programmed but may also involve memory from previous antigen exposure. Analysis of patients enrolled in a multicenter epidemiologic study of sarcoidosis in the United States (A Case Controlled Etiologic Study of Sarcoidosis) demonstrated that carriage of HLA-DRB1*1101 and HLADPB1*0101 alleles are risk factors for the disease[4]. A family based association study in black U.S. patients with sarcoidosis suggested that susceptibility or protection may be associated with certain HLA-DQB1 alleles[5]. The phenotype and outcome of sarcoidosis is probably influenced strongly by HLA genes. For example, carriage of HLA-DRB1*03 in Swedish subjects with sarcoidosis is strongly associated with the development of Lofgren syndrome and also with disease resolution[6,7].

The granuloma in sarcoidosis is characterized by a core of monocyte-derived epithelioid histiocytes and multinucleate giant cells with interspersed $CD4^+$ T lymphocytes. A minority of cells in or near the granuloma are $CD8^+$ T lymphocytes, fibroblasts, regulatory T cells, and B lymphocytes. The T-cell response is biased toward a Th1 phenotype, with important roles for, IFN-γ and interleukin-12 [8]. A variety of chemokines and cytokines have been associated with the granulomatous response in sarcoidosis, including tumor necrosis factor (TNF-a)[9,10]. The importance of TNF in sarcoidosis has been validated by studies documenting effectiveness of biologic TNF antagonists in sarcoidosis in treating some patients with sarcoidosis[11].

Sarcoidosis probably requires exposure to one or more exogenous antigens. Epidemiologic data, including reports of case-clustering, increased susceptibility with certain occupations, and transmissibility via transplant, all support this theory[12, 13]. Infectious agents have long been suspected as possible causes of sarcoidosis, but early studies failed to yield convincing support for various organisms. Using molecular techniques, there are now accumulating data suggesting that bacteria, such as mycobacteria or Propionibacterium acnes, may contribute to the disease[14]. It is quite possible that the triggering antigen varies depending on ethnicity, geographic location, and individual genetic background.



CLINICAL FEATURES

All kinds of combinations of organ involvement are possible[15]. With the exception of the pleura, the serous membranes are rarely involved but only the adrenals appear to be sacrosanct. No authenticated adrenal involvement has been reported apart from a suggested but unproven case in one series[16].Sarcoidosis would be relatively unimportant if not for the fact that it can affect vital organs in a chronic fashion, with the development of irreversible fibrosis resulting in functional impairment. Involvement of the eyes can lead to blindness and death can occur from cardiac, respiratory or renal failure.

Thoracic sarcoidosis

The hilar glands and the lungs are the organs most commonly affected in sarcoidosis and intrathoracic involvement is the most frequent accompaniment of sarcoidosis affecting other organs. By convention thoracic sarcoidosis is classified in four stages on the basis of the appearances of the chest radiograph. Stage I represents hilar lymphadenopathy, stage II hilar adenopathy plus pulmonary opacities and stage III pulmonary opacities only. Stage IV represents the development of irreversible pulmonary fibrosis. Enlargement of hilar lymph glands with or without paratracheal lymphadenopathy is the commonest manifestation of sarcoidosis. Usually, the glands are bilaterally and symmetrically involved, although rarely hilar enlargement may appear unilateral[17,18].

Most patients with pulmonary opacities present with stage II or stage III disease, although occasionally a patient presents with chronic progressive dyspnoea due to stage IV disease. There are often no symptoms but there may be those already outlined for hilar adenopathy. Many types of abnormality may be seen on the chest film and these may be classified as follows:

1) disseminated miliary lesions;
2) disseminated nodular lesions;
3) linear type of infiltration extending fan-wise from the hilum;
4) diffuse and confluent patchy shadows;
5) diffuse fibrosis;
6) diffuse fibrosis with cavitation 19;
7) diffuse ground-glass shadowing 20;
8) changes similar to chronic tuberculosis as regards location and distribution;
9) bilateral confluent massive opacities resembling areas of pneumonia;
10) Atelectasis

Of the varieties of pulmonary change, cavitation and atelectasis are the least common. Aspergillomas may rarely develop in cavities, apparently more commonly in men[21].

Extrathoracic sarcoidosis

Lymphatic system

The lymph nodes most frequently affected in sarcoidosis are those of the hilar and paratracheal groups. Of the superficial nodes, those of the right scalene group are most commonly affected but enlargement of any of the superficial nodes may be found.

Eyes

Ocular manifestations have been reported in as many as 25% of patients with sarcoidosis[22,23]. The eyes should be examined routinely, preferably with a slit lamp, in all cases since mild asymptomatic eye involvement may be commoner than is suspected. Uveitis is the most frequent manifestation of eye involvement causing symptoms. It develops acutely with pain in the eyes and misty vision in about one-third of patients, while the remainder show the chronic form that develops insidiously. Anterior uveitis is usual in self-limiting sarcoidosis, while posterior uveitis is typical of the chronic form of the disease. Acute

conjunctivitis, sometimes of the phlyctenular type, may occur particularly in early sarcoidosis and conjunctival biopsy may provide proof of the diagnosis. Keratoconjunctivitis sicca results in dryness of the eyes; a Sjögren like syndrome may be encountered if the salivary glands are also involved. The lacrimal glands may also be enlarged.

Skin

The most common skin manifestation in sarcoidosis is erythema nodosum, which in severe cases may be associated with prolonged fever[24]. Recurrent episodes of erythema nodosum may occur sometimes over many years[25]. Maculopapular eruptions, subcutaneous nodules, plaques and lupus pernio are other lesions that may be found. Sarcoidosis of the upper respiratory tract carries a 50% risk of the development of lupus pernio within 2–3 years[26].

Upper respiratory tract

Sarcoidosis of the upper respiratory tract is an uncommon but disabling manifestation of the disease affecting the nose, nasopharyngeal mucosa and the larynx[27,28,29]. The septum and inferior turbinates are most commonly involved, although sometimes the lesions are more widespread. Disease of the laryngeal and pharyngeal mucosa may coexist with, or be independent of, nasal lesions. Hoarseness, cough, dysphagia and dyspnoea secondary to upper airway obstruction may occur[30]. A patient presenting with sarcoidosis of the upper respiratory tract has a 50% chance of developing lupus pernio, although one feature may be present without the other. Nasal septal or palatal perforations may complicate untreated sarcoidosis of the upper respiratory tract.The Kveim test is almost always positive, and this assists in the differential diagnosis of granulomas in the upper respiratory tract, which includes Wegener's granulomatosis, tuberculosis and leprosy.

Alimentary system

Involvement of the salivary glands and liver is common, while affection of the pancreas and gastrointestinal tract is rare. Pancreatitis has been reported[31,32], and bloody ascites secondary to granulomatous involvement of the peritoneum has been described in two cases[33].

Uveoparotid fever

Uveoparotid fever was first described by Heerfordt in 1909 as a febrile illness characterized by uveitis and swelling of the parotids, accompanied frequently by facial palsy. At first thought to be a mild form of tuberculosis, it is now recognized as one of the curious combinations of organ involvement that can occur in sarcoidosis. Parotid enlargement is bilateral in more than half the cases and may be mistaken for mumps[34].

Nervous and endocrine systems

Sarcoidosis affecting the nervous system by infiltration osarcoid deposits may result in a variety of clinical pictures[35-53]:

1) peripheral neuropathy or mononeuritis multiplex;
2) cranial neuropathy, most commonly of the seventh cranial nerve (sarcoidosis is the commonest cause of bilateral facial nerve palsy);
3) lymphocytic meningitis, in which the cerebrospinal fluid shows pleocytosis, increased protein and decreased glucose levels;
4) meningoencephalitis;
5) space-occupying lesions;
6) epilepsy;
7) brainstem and spinal syndromes are rare but may masquerade as multiple sclerosis, amyotrophic lateral sclerosis or spinal tumour. Left recurrent laryngeal nerve palsy

due to compression of the nerve by enlarged mediastinal nodes has been reported as the presenting symptom of sarcoidosis.

CARDIAC

Cardiac disease, which usually presents as either congestive heart failure or cardiac arrhythmias, results from infiltration of the heart muscle by granulomas. Diffuse granulomatous involvement of the heart muscle can lead to profound dysfunction with left ventricular ejection fractions below 10%.

DIAGNOSIS

Sarcoidosis is defined as a multisystem granulomatous disorder of unknown cause. This usually warrants a tissue biopsy, although in special situations a presumptive diagnosis may be made based on clinicoradiographic findings alone. These situations include the presence of bilateral hilar adenopathy on the chest radiograph in an asymptomatic patient, Lofgren syndrome (erythema nodosum skin rash coupled with bilateral hilar adenopathy on chest radiograph and often fever and arthritis), Heerfordt syndrome (uveitis, parotiditis, and fever), and when a gallium-67 scan reveals uptake in the parotid and lacrimal glands (Panda sign) along with right paratracheal and bilateral hilar uptake (Lambda sign). Likewise, the presence of granulomas alone is also inadequate for the diagnosis of sarcoidosis. The diagnosis is established when clinicoradiographic findings are supported by histologic evidence of noncaseating granulomatous inflammation and other causes of granulomas and local reactions have been reasonably excluded.

Patients are usually evaluated for possible sarcoidosis based on two scenarios[54]. In the first scenario, a patient may undergo a biopsy revealing a noncaseating granuloma in either a pulmonary or an extrapulmonary organ. If the clinical presentation is consistent with sarcoidosis and there is no alternative cause for the granulomas identifiedthen the patient is felt to have sarcoidosis. In the second scenario, signs or symptoms suggesting sarcoidosis such as the presence of bilateral adenopathy may be present in an otherwise asymptomatic patient or a patient with uveitis or a rash consistent with sarcoidosis. At this point, a diagnostic procedure should be performed. For the patient with a compatible skin lesion, a skin biopsy should be considered. Other biopsies to consider could include liver, extrathoracic Iymph node, or muscle. In some cases, a biopsy of the affected organ may not be easy to perform (such as a brain or spinal cord lesion). In other cases, such as an endomyocardial biopsy, the likelihood of a positive biopsy is low. Because of the high rate of pulmonary involvement in these cases, the lung may be easier to approach by bronchoscopy. During the bronchoscopy, a transbronchial biopsy, bronchial biopsy, or transbronchial needle aspirate can be performed.

The endobronchial ultrasonography-guided (EBUS) transbronchial needle aspirate can assist in diagnosing sarcoidosis in patients with mediastinal adenopathy (stage 1 or 2 radiographic pulmonary disease), whereas transbronchial biopsy has a higher diagnostic yield for those with only parenchymal lung disease (stage 3).

For patients with negative pathology, positive supportive tests may increase the likelihood of the diagnosis of sarcoidosis. These tests include an elevated ACE level, which can also be elevated in other granulomatous diseases but not in malignancy. A positive PET scan can support the diagnosis if multiple organs are affected. A BAL is often performed during the bronchoscopy. An increase in the percentage of lymphocytes supports the diagnosis of sarcoidosis. The use of the Iymphocyte markers CD4 and CD8 can be used to determine the CD4/CD8 ratio of these increased Iymphocytes in the BAL fluid. A ratio of >3.5 is strongly supportive of sarcoidosis but is less sensitive than an increase in lymphocytes alone. Although in general, an increase in BAL lymphocytes is supportive of the diagnosis, other conditions must be considered.

The Kviem-Siltzbach procedure is a specific diagnostic test for sarcoidosis. An intradermal inj ection of specially prepared tissue derived from the spleen of a known sarcoidosis patient is biopsied 4-6 weeks a命er inj ection. If noncaseating granulomas are seen, this is highly specific for the diagnosis of sarcoidosis. Unfortunately, there is no commercially available Kviem-Siltzbach reagent, and some locally prepared batches have lower specificity. Thus, this test is of historic interest and is rarely used in current clinical practice

Treatment for Sarcoidosis

Anti-inflammatory treatment

-Acute disease

Glucocorticoids

Hydroxychloroquine

Methotrexate

-Chronic disease

Glucocorticoids

Methotrexate

Azathioprine

Leflunomide

Mycophenolate

Infliximab

Adalimumab

Hydroxychloroquine

-Refractory disease

Infliximab

Adalimumab

-Fibrotic disease

When criteria for treatment are met

Oxygen therapy

Lung transplantation

Pulmonary rehabilitation

REFERENCES

1) NHLB I. June 14,2013.Retrived 28 march 2016.
2) Calabrese LH, Kirchner E, Shrestha R. Rheumatic complications of human immunodeficiency virus infection in the era of highly active antiretroviral therapy: emergence of a new syndrome of immune reconstitution and changing patterns of disease. Semin Arthritis Rheum 2005;35:166–174.
3) Moller DR, Chen ES. Genetic basis of remitting sarcoidosis: triumph of the trimolecular complex? Am J Respir Cell Mol Biol 2002;27:391–395.
4) Rossman MD, Thompson B, Frederick M, Maliarik M, Iannuzzi MC,
5) Rybicki BA, Pandey JP, Newman LS, Magira E, Beznik-Cizman B, et al. HLA-DRB1*1101: a significant risk factor for sarcoidosis in blacks and whites. Am J Hum Genet 2003;73:720–735.
6) Rybicki BA, Maliarik MJ, Poisson LM, Sheffer R, Chen KM, Major M, Chase GA, Iannuzzi MC. The major histocompatibility complex gene region and sarcoidosis susceptibility in African Americans. Am J Respir Crit Care Med 2003;167:444–449.
7) Grunewald J, Eklund A. Lofgren's syndrome: human leukocyte antigen strongly influences the disease course. Am J Respir Crit Care Med 2009;179:307–312.
8) Grunewald J, Brynedal B, Darlington P, Nisell M, Cederlund K, Hillert J, Eklund A. Different HLA-DRB1 allele distributions in distinct clinical subgroups of sarcoidosis patients. Respir Res. 2010;11:25.
9) Moller DR, Forman JD, Liu MC, Noble PW, Greenlee BM, Vyas P,Holden DA, Forrester JM, Lazarus A, Wysocka M, et al. Enhanced expression of IL-12 associated with Th 1 cytokine profiles in active pulmonary sarcoidosis. J Immunol 1996;156:4952–4960.
10) Ziegenhagen MW, Rothe E, Zissel G, Muller-Quernheim J. Exagerated TNFalpha release of alveolar macrophages in corticosteroid resistant sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis 2002;19:185–190.
11) Baughman RP, Strohofer SA, Buchsbaum J, Lower EE. Release of tumor necrosis factor by alveolar macrophages of patients with sarcoidosis. J Lab Clin Med 1990;115:36–42.
12) Baughman RP, Drent M, Kavuru M, Judson MA, Costabel U, Du BR, Albera C, Brutsche M, Davis G, Donohue JF, et al. Infliximab therapy in patients with chronic sarcoidosis and pulmonary involvement. Am J Respir Crit Care Med 2006;174:795–802.
13) Sundar KM, Carveth HJ, Gosselin MV, Beatty PG, Colby TV, Hoidal JR. Granulomatous pneumonitis following bone marrow transplantation. Bone Marrow Transplant 2001;28:627–630.
14) Milman N, Andersen CB, Burton CM, Iversen M. Recurrent sarcoid granulomas in a transplanted lung derive from recipient immune cells. Eur Respir J 2005;26:549–552.
15) Eishi Y, Suga M, Ishige I, Kobayashi D, Yamada T, Takemura T, Takizawa T, Koike M, Kudoh S, Costabel U, et al. Quantitative analysis of mycobacterial and propionibacterial DNA in lymph nodes of Japanese and European patients with sarcoidosis. J Clin Microbiol 2002;40:198–204.
16) James DG. Diagnosis and treatment of sarcoidosis. Br Med J 1956; 2: 900.
17) Mayock RL, Bertrand P, Morrison CE, Scott JH. Manifestations of sarcoidosis. Analysis of 145 patients with a review of 9 series selected from the literature. Am J Med 1963;35: 67.
18) Spann RW, Rosenow EC, Deremee RA, Miller WE. Unilateral hilar or paratracheal adenopathy in sarcoidosis: a study of 38 cases. Thorax 1971; 26: 296.
19) Williams MJ. Sarcoidosis presenting with unilateral hilar lymph node enlargement. Scott Med J 1961; 6: 18.
20) James DG. Erythema nodosum. Br Med J 1961; 1: 853.

21) Lofgren S. The concept of erythema nodosum revised. Scand J Respir Dis 1967; 48:348.
22) Sones M, Israel HL. Course and prognosis of sarcoidosis. Am J Med 1960; 29: 84.
23) Ainslie D, James DG. Ocular sarcoidosis. Br Med J 1956; 1: 954.
24) Cowan CL. Ocular sarcoidosis. J Natl Med Ass 1959; 51: 371.
25) James DG. Ocular sarcoidosis. Am J Med 1959; 26: 331.
26) Nielsen RH. Ocular sarcoidosis. AMAArch Ophthalmol 1959; 61: 455.
27) Nolan JP, Klatskin G. The fever of sarcoidosis. Ann Intern Med 1964; 61: 455.
28) MacFarlane JT. Recurrent erythema nodosum and pulmonary sarcoidosis. Postgrad Med J 1981; 57: 525.
29) Neville E, Mills RGS, Jash DK et al. Sarcoidosis of the upper respiratory tract and its association with lupus pernio. Thorax 1976;31: 660.
30) Neville E, Mills RGS, James DG. Sarcoidosis of the upper respiratory tract and its relation to lupus pernio. Ann N Y Acad Sci 1976; 278:416.
31) Bower JS, Belen JE, Weg JG, Dantzker DR. Manifestations and treatment of laryngeal sarcoidosis. Am Rev Respir Dis 1980; 122: 325. 31. Tsou E, Romano MC, Kerwin DM et al. Sarcoidosis of anterior mediastinal nodes, pancreas and uterine cervix: three unusual sites in the same patient. Am Rev Respir Dis 1980; 122: 333.
32) McCormick PA, Malone D, Fitzgerald MX, Fitzgerald O. Pancreatitis in sarcoidosis. Br Med J 1985; 290: 1472.
33) Wheeler JE, Rosenthal NS. Bloody ascites in sarcoidosis. Chest 1985; 88: 917.
34) Siltzbach LE. Kveim test in sarcoidosis. JAMA 1961; 178: 476.
35) Aszkanazy CL. Sarcoidosis of the central nervous system. J Neuropathol 1952; 11: 392.
36) Campbell IW, Short AIK, Douglas AC. Hypothalamic manifestations of sarcoidosis–with particular reference to hypothalamic hypothyroidism. In: Jones Williams W, Davies BH, eds. Proceedings of the Eighth International Conference on Sarcoidosis and Other Granulomatous Diseases. Cardiff: Alpha Omega, 1980: 579.
37) Colover J. Sarcoidosis with involvement of the central nervous system. Brain 1948; 71: 451.
38) Cummins SD, Clark DH, Gandy TH. Boeck's sarcoid of the thyroid gland. Arch Pathol 1951; 51: 68.
39) Daum JJ, Canter HG, Katz S. Central nervous system sarcoidosis with alveolar hypoventilation. Am J Med 1965; 38: 893.
40) Douglas AC, Maloney AFJ. Sarcoidosis of the central nervous system. J Neurol Neurosurg Psychiatry 1973; 36: 1024.
41) Fazlullah S. Sarcoidosis with involvement of the nervous system. Dis Chest 1962; 41: 685.
42) Goodson WH. Neurological manifestations of sarcoidosis. South Med J 1960; 53: 1111.
43) Hook O. Sarcoidosis with involvement of the nervous system: report of nine cases. AMAArch Neurol Psychiatry 1954; 71: 554.
44) Jefferson M. Sarcoidosis of the nervous system. Brain 1957; 80: 540.
45) Jefferson M. The nervous system in sarcoidosis. Postgrad Med J 1958; 34: 259.
46) Jonasson JV. Sarcoidosis of the nervous system: report of four cases with interesting signs. Acta Psychiatr Scand 1960; 35: 182.
47) Matthews WB. Sarcoidosis of the nervous system. Br Med J 1959; 1: 267.
48) Nora JR, Levitsky JM, Zimmerman HJ. Sarcoidosis with panhypopituitarism and diabetes insipidus. Ann Intern Med 1959; 51: 1400.
49) Schonell ME, Gillespie WJ, Maloney AEJ. Cerebral sarcoidosis. Br J Dis Chest 1968; 62:195.

50) Thompson JR. Sarcoidosis of the central nervous system: report of a case simulating intracranial neoplasm. Am J Med 1961; 31:977.
51) Walker AG. Sarcoidosis of the brain and spinal cord. Postgrad Med J 1961; 37: 431.
52) El-Kassimi FA, Ashour M, Vijayaraghavan R. Sarcoidosis presenting as recurrent laryngeal nerve palsy. Thorax 1990; 45: 565.
53) Jaffe R, Bogomolski-Yahalom V, Kramer MR. Vocal cord paralysis as the presenting symptom of sarcoidosis. Respir Med 1994; 88:633.
54) Harrison 19th edition 2205-2212