Comments on Systemic Sarcoidosis

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The precise incidence of sarcoidosis is not known. It has been estimated that over 1,000 cases have been reported by 1948. Between 1936 and 1948, 25 cases were seen in Pennsylvania Hospital and between 1947 and 1952, 21 cases were seen in the Jefferson Hospital. Among some 628,000 residents of Philadelphia of all ages, sex and color examined roentgenologically for tuberculosis during the past 10 years by the Philadelphia Tuberculosis and Health Association slightly over 2 per 100,000 presented roentgenologic findings compatible with sarcoidosis, later proved by biopsy. Although the disease is world-wide in distribution, it is more prevalent among the rural folk living in the temperate zone. In the United States, for some reason, the disease is more common in the southeastern portion, predominantly in the rural rather than in metropolitan areas. In an epidemiologic study of 226 cases of sarcoidosis in military personnel by Michael et al., 88 per cent came from the southern United States. This was true for both Negro and white groups. Even among the Negro group those born in the South showed an incidence of 25 per 100,000 inductees, as compared to an incidence of 1 per 100,000 in those with Northern birthplace and 6 per 100,000 in those from the west. This suggests that whatever the etiologic factor may be, it appears more concentrated in the southern United States. The disease has been noted in Japan, Australia, South America and South Africa. In Europe the Scandinavian countries reported most of the cases.

People of all ages are affected. Predominantly, however, it appears to be a disease of early adult life between the third and fourth decades. In the United States there is no doubt that the condition is more prevalent in Negroes; in some studies the incidence in Negroes was 16 times as great as in whites.

This disease was first described in 1875 by Hutchinson. The patient was a woman named Mortimer, aged 65. The lesions consisted of a number of patches on her cheeks and back of her upper arms. The patches were raised and sharply defined on skin otherwise healthy. They were red and not ulcerated, but showed some scales. Gradually the lesions spread over the entire face. He named the condition "Lupus Vulgaris Multiplex Non-Ulcerans et Non-Surpliginosus". Fourteen years later Besnier reported the second case.

Boeck of Norway reported (1894) a 36-year-old police officer in good health except for skin disease on the brow, spreading to other parts of

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the face, limbs and trunk. He removed two skin nodules each about the
size of a pea and described the histologic features of sarcoid. Curiously
enough, the autopsy specimens from this same patient were examined in
1947; no evidence of sarcoid was found\(^5\) anywhere. The patient died at
the age of some 80 years of hypernephroma. Heerfordt first noted fever,
uvritis, parotitis and paralysis of the facial nerve. Bruins Slot suggested
that uveoparotid fever was a form of sarcoidosis. Schaumann noted the
disease was primarily a systemic condition and Jungling first noted in-
volvement of the bones of the hands. The term sarcoid proposed by Boeck
is derived from two Greek roots meaning “flesh” and “form”.

The organs most frequently involved are lymph nodes, lungs, liver, spleen
and skin. Involvement of the heart, small bones of the hands, stomach,
intestines, kidneys, bladder, pituitary and thyroid glands, eyes, voluntary
muscles and central nervous system has been noted.

Regardless of the tissue or organ involved, the basic lesion is always the
same. It is a sharply delineated granuloma composed of uniform polyhedrol
cells with abundant acidophilic cytoplasm and large, ovoid, vesicular nuclei.
As the lesion matures, a narrow rim of two or three layers of fibroblasts
encircle it while epithelioid cells elongate and become concentrically
arranged. Regression by fibrosis then occurs, beginning as a fibrotic process
between and around the individual granulomas. The fibrous tissue rapidly
becomes compact, hyalinizes and forms a dense scar in which only a
suggestion of the previous tubercle remains. Numerous giant cells are
found within these lesions.

Some giant cells carry inclusion bodies, the Schaumann body and the
spiculated body of “asteroids”. Schaumann bodies are found in 3 per cent
and “asteroids” in 2 per cent. Neither of the inclusion bodies is specific
of this disease. Schaumann bodies are seen in the lymph nodes of lympho-
pathia venereum and in giant cells in the lymph nodes draining an area
of regional ileitis. Asteroids occur in tuberculosis, leprosy, histoplasmosis,
schistosomiasis and lipoidal granuloma. Occasional vasculization occurs
in the giant cells.

Necrosis in sarcoidosis has been described as “fibrinoid” and is strongly
eosinophilic. A few intact lymphocytes may occur about the periphery of
the necrotic area, but otherwise the necrosis is usually acellular. Total
absence of cells and cellular debris with fibrillar zones of necrosis distin-
guishes this from the caseation of tuberculosis. In no case of sarcoidosis
has Mycobacterium tuberculosis been found.

Enlarged lymph nodes, cough, dyspnea, weight loss, skin manifestation,
low grade fever, malaise and weakness, deformity of the hands when the
bones are involved, conjunctivitis, poor vision, and facial paralysis are the
symptoms and signs. Quite frequently the condition is suspected following
roentgenological examination of the chest prior to employment. In such
cases, despite pronounced changes in the lungs, the person may not have
any symptom.

The cause of sarcoidosis is still unknown. Whether the disease is an
atypical form of tuberculosis is one of the most controversial issues in
medicine. That it is some form of tuberculosis is more generally accepted in Europe than in America. The strongest evidence against tuberculosis as an etiologic factor is that in addition to the usual negative reaction to the tuberculin test, in no unequivocal case of sarcoidosis was Mycobacterium tuberculosis ever found. Mycobacterium leprae, Treponema pallidum, Protozoa, viruses, fungi, helminths, beryllium, foreign bodies such as paraffin, crystalline material, silica, soil, silk, wool and others and certain hyperergic states of the victim with arteriolar lesions, as well as neoplastic origin and collagen disease are sometimes considered as possible causes.

Regarding some of the methods of diagnosis, a punch biopsy of the liver by means of Vim-Silverman needle and lung biopsy may be mentioned. Liver biopsy is of particular importance when the skin and superficial lymph nodes are not involved. The chief objections to needle biopsy are that serious, and occasionally fatal, complications may follow and that the small samples of tissues obtained may fail to include lesions, although actually present in the liver. The dangers are negligible, provided the procedure is carried out skillfully and precautions are taken in the selection and postoperative care of patients. There was no fatality in 650 biopsies done by Klatskin. He showed close resemblance in morphology between the hepatic lesions of sarcoidosis and those of tuberculosis, erythema nodosum and brucellosis. Granulomata in tuberculosis and brucellosis exhibited greater incidence of caseation and necrosis of the tissues, and inflammatory reaction of the tissues surrounding the granulomata, but most of the lesions could not be differentiated on histological appearance alone.

Needle biopsy of the liver has definite value in confirming the diagnosis of sarcoidosis, despite the uncertainties due to the resemblance of the tissue reactions in sarcoidosis with that seen in other diseases. In Scandinavia biopsy of the tonsillar tissues is popular.

Lung biopsy apparently is a safe procedure. Under local anesthesia a small incision is made in the anterior surface of the thorax, usually between the third and fourth ribs at the anterior axillary line. Then the patient is made to inhale oxygen under positive pressure. In so doing the increased intrapulmonary pressure forces the lung to protrude through the incision. That part of the lung is tied and incised. Tissue is fixed in formalin and stained in the usual manner and examined. In over 24 pulmonary biopsies done during the past year in Jefferson Hospital by Allbritten, there was no case of pneumothorax, empyema or other complication. Patients were able to leave the hospital in 24 hours, in perfect comfort.

The so-called Nickerson-Kveim test, which is an intradermal test using 0.15 cc. of suspension of sarcoid nodules in isotonic solution of sodium chloride, is again a controversial one. In some hands this test has been satisfactory; for example, it was found to be 80 per cent positive in the series studied by Slitzbach. On the other hand, in Jefferson Hospital the test has been unreliable and, as a matter of fact, it is not used as a routine procedure in the study of sarcoidosis. One of the disadvantages of this test is that even in a proved case of sarcoidosis a definite reaction does not
take place for weeks to months. Sones\textsuperscript{6} carried out studies on immunological reactions in sarcoidosis on 38 patients and found that patients with sarcoidosis reacted less often than controls, not only to tuberculin but also to pertussis agglutinogen, mumps virus, and oldomycin.

Hyperglobulinemia, hypercalcemia, hemolytic anemia, neutropenia, thrombocytopenia and increased sedimentation rate and pulmonary insufficiency may occur.

Treatment of sarcoidosis is unsatisfactory. Vitamin D\textsubscript{2}, BCG vaccination, streptomycin, nitrogen mustard, urethane, tuberculin and anti-leprol have been used, but found to be of no value. Cortisone, 100 to 150 mg. daily in divided doses for a month to three months may be helpful. Upon termination of the therapy, relapses follow in the majority of cases.

Sodium intake should be restricted to 200 mg. a day for hospitalized patients and 500 mg. for ambulatory patients. A potassium supplement may be given in the form of the chlorides, 3 gm. daily. In the cases of ocular lesions it is imperative that the drug be used. In uveitis, particularly if the anterior segments are involved, drops of cortisone may be instilled directly into the eye or underneath the conjunctiva. However, if the posterior segments are involved, then ACTH intravenously, or cortisone orally in tablet form, is used. The effect of these treatments appears to be satisfactory.

As far as prognosis is concerned, many seem to recover spontaneously only to relapse later on. It has been estimated, however, that about 30 per cent recover permanently. This again is open to question. Some develop congestive heart failure resulting from cor pulmonale and about 25 per cent of them develop fatal pulmonary tuberculosis. In such a case there is always a doubt whether the condition was not tuberculosis from the beginning.

**SUMMARY**

Sarcoidosis is a disease of unknown cause. The basic morbid anatomy regardless of the organ or tissue involved is the epithelioid cell tubercle without necrosis, having refractile or calcified inclusion bodies in the giant cells.

Lesions are usually widely disseminated. The tissues most frequently involved are lymph nodes, lung, liver, spleen, skin, eyes and bones, particularly of the hands. The heart, striated muscles, stomach, intestines, kidneys, bladder, pituitary and thyroid glands, and central nerves may also be involved.

The clinical course is usually chronic with minimal or no constitutional symptoms; however, there may be acute episodes of fever and malaise with or without signs or symptoms referable to the tissues and organs involved.

The intracutaneous tuberculin test is usually negative; the plasma globulins are often increased.

The outcome may be clinical recovery with radiographic evidence of residue, or impairment of function of organs involved, or a continued
chronic course of the disease. Treatment is unsatisfactory. Prognosis is uncertain.

RESUMEN

La sarcoidosis, es una enfermedad de causa desconocida. La anatomía patológica básica sin tener en cuenta el órgano o tejido comprometidos, es el tubérculo de células epitelioides sin necrosis, que contiene cuerpos de inclusión refractiles o calcificados en las células gigantes. Las lesiones habitualmente están ampliamente diseminadas.

Los tejidos más frecuentemente afectados son los ganglios linfáticos, el pulmón, el hígado, el bazo, la piel, los ojos y los huesos especialmente, los de las manos. El corazón, los músculos estriados, estómago, intestinos, riñones, vejiga, la pituitaria, la tiroides y el sistema nervioso central, pueden también ser afectados.

La evolución clínica, es generalmente crónica con síntomas generales mínimos o ningunos; sin embargo, puede haber episodios agudos con fiebre, malestar con o sin síntomas referibles a los tejidos u órganos afectados.

La reacción intracutánea de tuberculina, es habitualmente negativa.

Las globulinas en el plasma, a menudo están aumentadas.

El resultado final, puede ser la recuperación clínica con evidencias de residuos radiográficamente o bien hay una evolución crónica de la enfermedad. El tratamiento no es satisfactorio. El pronóstico es incierto.

RESUME

La sarcoidose est une maladie de cause inconnue. Le substratum anatomique de la lésion, indépendamment du viscère ou du tissu atteint est le tubercle épithélioide sans nécrose avec dans les cellules géantes, des inclu-
sions de corps réfringents ou calcifiés. Les lésions sont habituellement largement disséminées. Les tissus le plus souvent atteints sont les ganglions, le poumon, le foie, la rate, la peau, les yeux et les os, en particulier ceux de la main. Le coeur, les muscles striés, l'estomac, les intestins, les reins, la vésicule biliaire, les ganglions hypophysaires, et thyroïdes ainsi que le système nerveux central peuvent être également atteints.

L'allure clinique est généralement chronique, ne s'accompagnant que de symptômes minimes ou peu caractéristiques. Toutefois, il peut y avoir des épisodes aigus, de la fièvre et des troubles généraux comportant ou non des symptômes dus à l'atteinte de certains tissus ou de certains organes.

Habituellement, les réactions tuberculiniques sont négatives. Souvent, il y a augmentation fréquente des globulines plasmatiques.

L'évolution peut se faire vers une guérison clinique s'accompagnant de séquelles radiographiques ou vers un trouble fonctionnel des organes atteints ou encore vers la chronicité de l'affection. Aucun traitement ne donne satisfaction. Le pronostic est incertain.

REFERENCES