RARITY OF SARCOIDOSIS IN MALAYSIA

REPORT OF A CASE

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Sarcoidosis is not a rare disease in Western countries. Sarcoid skin lesions were first described in the latter half of the nineteenth century by Jonathan Hutchinson in his book 'Clinical Surgery' (1875). He later described the lesions in more detail under the title of 'Mortimer's Malady' (1898). Similar skin lesions were described by the French dermatologist Besnier as lupus pernio. Later on, Boeck (1899) described the histological detail and from a resemblance to sarcoma, coined the term SARCOID. Although it is now known that the two diseases are entirely unrelated, the term has remained to be used. Heerfordt (1909) first described 'fibris uveo-parotidea subschronica' (quoted by Harden), however it was not until 1936 to 1938 that this condition was firmly established as a form of sarcoidosis following the papers of Longcope and Pearson (1937). Mickulicz (1937) described the lachrymal and salivary gland involvement that may occur in this condition, but it was Schaumann (1936) that first drew attention to the view that sarcoidosis is a diffuse systemic affection that may present with clinical features referable to almost any organ. Engle (1953) made post mortem studies in a group of twenty seven patients and these are described by him in great detail with excellent illustrations.

A recent analysis by Cummings et al in America (1959), disclosed 1,194 cases of sarcoidosis in a five-year interval in Veterans' Administration Hospitals, and according to Wijkstrom (1956), chest X-ray surveys of one million inhabitants of Sweden between 1950 and 1954 detected half as many cases of sarcoidosis as those with tuberculosis. From the experience of the large mass X-ray campaigns in the State of Singapore conducted by the Ministry of Health and the Singapore Anti-Tuberculosis Association, no cases of sarcoidosis were seen among 241,636 persons of all races, (Chinese, Malays, Indians, Eurasians, etc.) above the age of fourteen years, domiciled in Singapore. (Table 1, Yeoh Seang Ann and Sen Gupta, 1963).

TABLE 1

MASS X-RAY SURVEYS IN SINGAPORE, 1963.

Year	Government Survey	S.A.T.A. Survey	Total
1958	54,812	Nil	54,812
1959	2,838	16,886	19,724
1960	16,321	16,484	32,805
1961	50,352	17,772	68,124
1962	50,179	15,992	66,171
	174,502	67,134	241,636

Moreover, in the experience of the Singapore Anti Tuberculosis Association Clinic which has seen an average of 2,000 new cases a year since 1955, no cases of sarcoidosis have been found (Sen Gupta, 1963). It is therefore an established fact that sarcoidosis is extremely rare in Singapore. With regard to the rest of Malaysia and South East Asia, no cases of sarcoidosis have been described in the literature of this region. However, we are of the opinion that sarcoidosis does exist locally perhaps more commonly than is realised and that cases may have been missed in the past, as the case herewith reported and the following discussion would tend to suggest. In view of this fact, the report of a case would not appear out of place.

CASE REPORT

An Indian male born in Singapore. V. J., aged 47 years, an inspector of hawkers by occupation, was first seen in March, 1958. He was admitted then for generalised weakness and lassitude. Investigations revealed that he was a diabetic and it was thought that the symptoms were manifestations of the disease. He was treated and controlled with injections of 32 units of protamine zinc insulin daily. He also gave the history that when he was about 8 years of age his older brother was discovered to have leprosy at the age of 11 and was treated at an institution for two years before returning home.

In January 1960, he complained of praecordial pain which radiated down the left arm, forearm and hand. Examination showed that he was moderately obese. His blood pressure was 130/90. His cardiovascular and respiratory systems were normal. Scaly, whitish, raised, circular eruptions were seen over his forehead, anterior chest wall and back, and these were diagnostic of psoriasis. Subsequent investigations including an electrocardiogram, did not confirm the presence of cardiac disease and a diagnosis of diabetes mellitus with psoriasis was made. The patient was put on a 1,000 Calorie reducing diet, salicylic acid tar paste and control of his diabetes was attained with Tolbutamide (Rastinon) 1 Gram t.d.s.

His next admission was in July, 1960. This time he complained of pain in the small joints of his hands and feet. He also had vague epigastric discomfort which was unrelated to meals. He was afebrile; blood pressure was 150/90. The joints of his hands and feet were limited in movement because of pain but there was no visible swelling. Cardiovascular, respiratory, and nervous systems were normal. His liver and spleen were not palpable. Marks of the skin lesion were still present. Radiological examinations of his hands and spine did not show any abnormality. Psoriasis with arthropathy was diagnosed. The patient was put on acetylsalicylic acid gr. 30 t.d.s. and prednisolone 10 mg. t.d.s. There was not much improvement on this regime and after a period of ten days, prednisolone was replaced by triamcinolone 4 mg. t.d.s. On this treatment the symtoms subsided.

In August 1960, the patient again had severe pain in the wrist, joints of the hands and feet and the lumbar region. Apart from the scaly skin lesions which were still present, physical examination did not show any abnormality. The history pointed to a strong psychogenic factor and on consulting a psychiatrist, a diagnosis of endogenous depression was made. The patient was put on isocarbozazid (Marplan) 10 mg. t.d.s. in addition to the other medications.

The patient was never really free from complaints since and had persistent, migratory, vague pains with occasional cough. In May 1962, he found that his vision was getting dim and he had excessive lachrimation. He was sent to see the eye surgeon who reported that his uveal tract and fundi were normal. He was put on oral antibiotics and aureomycin eye ointment. Whilst under this treatment, he suddenly developed bilateral parotid swellings. At first it was thought that he had mumps, but when it was observed that the parotid swellings varied enormously in size from day to day, and in addition, that he had by then developed an enlarged liver of two fingers-breadth below the right costal margin, and also small mobile lymph nodes in both cervical regions, the diagnosis of sarcoidosis was thought of for the first time. Biopsy of the scalene node, parotid gland, liver and skin eruptions were done. Of these the histological picture in the scalene node, parotid gland and liver were typical of sarcoidosis. (Figures 1, 2, 3, & 4). Epithelioid follicles with giant cells, but without caseation or acid-fast bacilli were seen. The skin speciment showed some non-specific granulation tissue. Other laboratory data include: -

Intradermal old tuberculin tests (1: 1,000 & 1: 100): Both gave negative results. (A highly uncommon finding amongst adults locally.)
Blood Khan and Wasserman Tests: Negative.
Blood sedimentation rate: 3 mm/hr.
Haemoglobin: 15.7 Grams %.
Total white count: 6,000/cu mm.

Differential Count:	Neutrophils:	71%
	Lymphocytes:	21%
	Eosinophils:	4%
	Monocytes:	4%
	Basophils:	0%

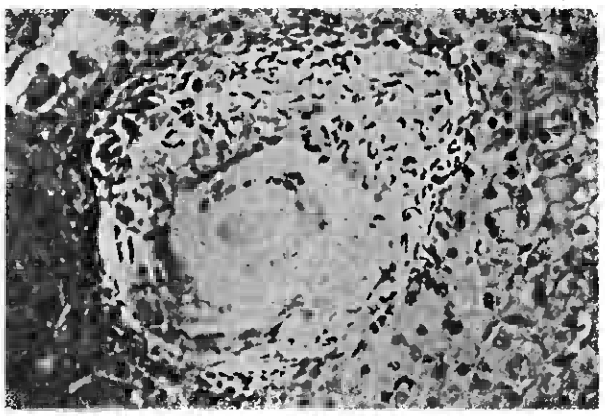

Fig. 1. LIVER. Magnification 900. Note peculiar giant cell in a typical sarcoid nodule.

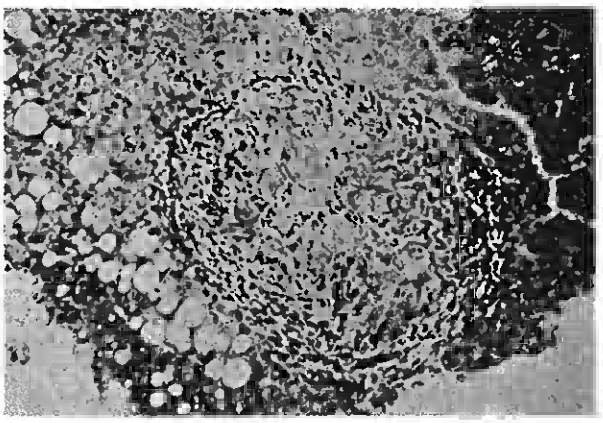

Fig. 2. LIVER. Magnification 225. Sarcoid lesion with no caseation. Note the good demarcation from the surrounding normal liver parenchyma.

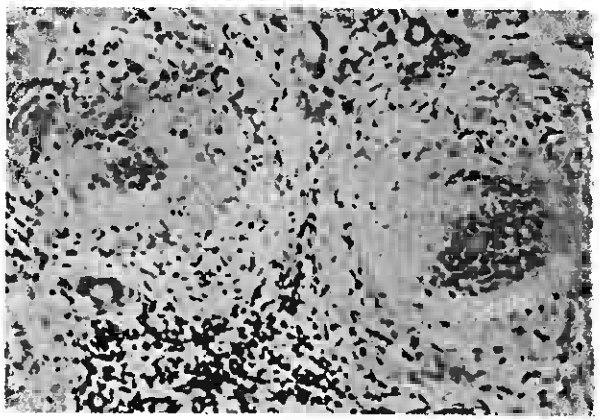

Fig. 3. PAROTID GLAND. Magnification 900. Note the foreign-body type of giant cell with numerous, randomly placed nuclei.

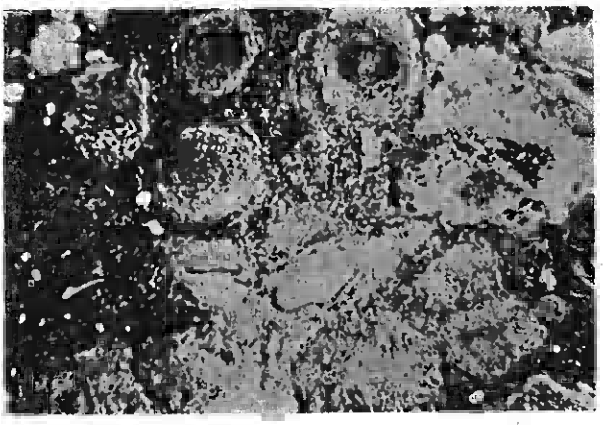

Fig. 4. PAROTID GLAND. Numerous sarcoid units with not the slightest evidence of caseation.

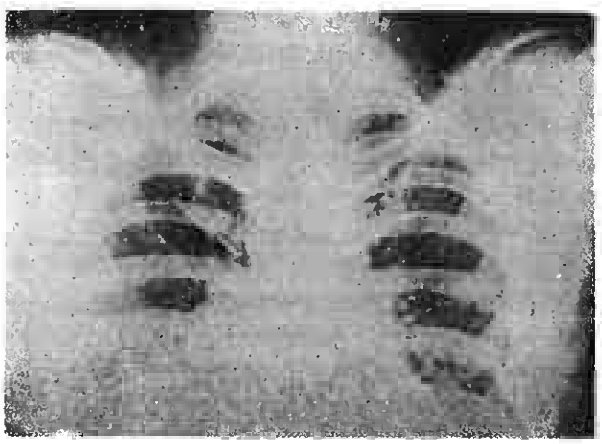

Fig. 5. X-ray Chest. Note the large circular opacity in the right hilum.

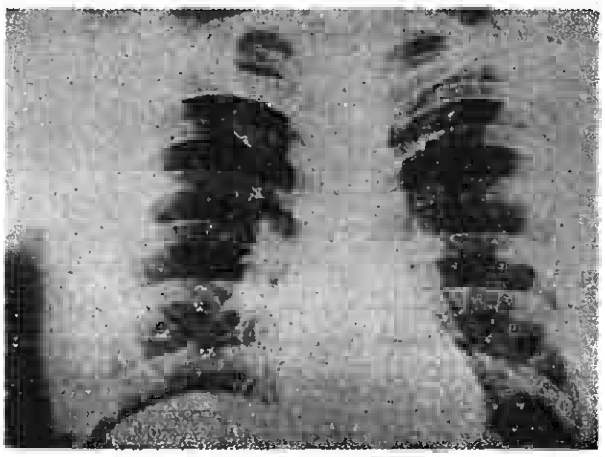

Fig. 6. X-ray Chest. Note the almost complete disappearance of the opacity.

X-ray of the chest: This showed the presence of transient opacities in the hilar region. (Figures 5, 6 & 7)

Serum Calcium: 10.9 mg %.

Urinary excretion of calcium in 24 hours: 534 mg.

(Normal range: 100-300 mg.)

From the above clinical and laboratory findings, a diagnosis of sarcoidosis was made. The patient was then put on prednisolone 10 mg. t.d.s. from June 1962 till December 1962, when the dosage was reduced to 5 mg. t.d.s. He was then maintained on 2.5 mg. t.d.s. and when last seen in January 1963, was doing quite well.

DISCUSSION

In this patient, the most prominent clinical finding, and indeed the one that prompted the diagnosis, was the swelling of the parotid glands. When once thought of, the diagnosis was easily established, for in addition to a host of positive symptoms and signs viz:- weakness, malaise, loss of weight, aches in the joints, blurring and dimness of vision, bilateral parotid swellings and hepatomegaly, laboratory and special investigations gave the following positive results. Biopsy of the liver, scalene nodes and parotid gland showed the presence of sarcoid follicles, without caseation and without demonstrable acid-fast bacilli. This alone is enough to have established the diagnosis as stipulated by Israel and Sones. (See under Diagnosis). But in addition to this, further positive data were present. These include the hilar lymphadenopathy (demonstrated radiologically), the negative reactions to intradermal old tuberculin (a highly unusual feature of inhabitants over the age of ten years in Singapore), and an increased urinary excretion of calcium.

In view of the history of contact with leprosy in this case, the possibility that the condition in our patient may be a special mode of reaction to leprosy has to be considered. Foreign-body granulomas also present a sarcoid-like picture and sarcoid-like infiltrations are known to occur in tuberculosis, leprosy and syphilis. However the features present in the patient bear not the slightest resemblance to the usual forms of these conditions in Singapore.

Whether the diabetes mellitus present in this patient is related to sarcoid involvement of the pancreatic islets is a matter of conjecture, and this has yet to be reported in world literature.

From the one specimen of the skin lesion that was obtained, non-specific granulation tissue was seen. The possibility arises that the case may have been one of the specific diseases commonly confused with sarcoidosis. Of the common diseases in this part of the world that may present microscopic features which simulate sarcoidosis, only syphilis, tuberculosis and leprosy need be considered, and these can be excluded on the basis of the absence of clinical features of these diseases, the negative Khan and Wasserman tests, the low blood sedimentation rate, and the negative reactions to old tuberculin.

The features of this case are fairly typical of sarcoidosis. However in view of the hesitancy to diagnose this conditon and its seeming rarity in this region, a brief review of the disease is presented in the hope that it may be better known and recognised.

AETIOLOGY

Many hypotheses as regards the aetiology of sarcoidosis have been put foreward. In general these may be put into three groups.

The Tuberculosis Hypothesis

That sarcoidosis is in some way related to tuberculosis is shown firstly by the fact that histologically the lesions do have some semblance of the tuberculous follicle, and secondly, evidence has accumulated that patients dying of sarcoidosis do show signs of frank tuberculosis. Against this hypothesis are the following facts. Tubercle bacilli have never been demonstrated in the sarcoid follicle, and caseation which is a constant feature of tuberculosis, occurs but very rarely in the sarcoid follicle. It is also known that patients with sarcoidosis often show a negative intradermal tuberculin reaction.

Other infections (? Viral) as a cause

A number of known pathogens have been incriminated at various times. The resemblance of the sarcoid lesions to those of tuberculoid leprosy has long been recognised. Other

diseases for example syphilis, coccidiomycosis, brucellosis and ascariasis have been shown as having, in some instances, the histological characteristics of sarcoidosis. Freiman (1948) has discussed at great length the significance of these sarcoid-like, histological lesions in known diseases, and he thinks that the sarcoid-like follicle, not to be confused with sarcoidosis as a disease entity, is just one of the ways in which the body reacts to the presence of various pathogens and foreign agents that come into contact with the body. Thus the appearance of the histological sarcoid-like follicle is common not only to the above mentioned diseases, but is also a feature of such diseases as silicosis, berylosis, Hodgkin's disease and regional ileitis. More recently, Lofgren and Lundback (1950) isolated a virus of the influenza-mumps-Newcastle group from six cases of sarcoidosis and this has stimulated further interest in this hypothesis.

Sarcoidosis as an allergic reaction

That sarcoidosis has some relationship to the pine tree, possibly as an allergic reaction to pine pollen, was first suggested by Cummings et al (1956) who pointed out that areas with a high incidence of sarcoidosis in the United States of America coincide with areas of dense pine forrests. They (1959) also drew attention to certain acid-fast properties of pine pollen and to similarities between substances in pine pollen and the tubercle bacillus. Baer (1960) had further evidence of this relationship in his study of a family of twelve siblings, in which four had sarcoidosis. He found that all the patients with sarcoidosis chewed pine pitch when they were young. However, Richert (1959), by oral ingestion of pine pollen himself, has shown that he did not develop sarcoidosis after taking 720 mg. of loblolly pine in 30 divided doses between March 7th and May 9th, 1959. The only noticeable effect was, according to him, a mild irritation of the bowels with a tendency to loose stools. Up till June, 1959, no radiological or clinical evidence of sarcoidosis was found. Skin tests using an antigen prepared from loblolly pollen gave negative results, and there was no alteration of the the strength of reaction to old tuberculin. However, Dr. Richert agreed that this simple experiment did not prove that pine pollen could not cause sarcoidosis.

From this brief summary it can be seen that the aetiology of sarcoidosis is far from being settled and much is still being done in the search for the final answer.

Pathology

The disease is essentially a benign one and Richer and Clark (1949) could attribute death directly to the disease in only three cases out of 22 autopsies of patients with sarcoidosis. Evidence is being accumulated to show that the lung is primarily affected after which the disease process is spread to other organs via the lymphatics and blood stream.

The smallest histological unit is the tuberculoid lesion which is composed of epithelioid histiocytes and giant cells. At the periphery of this nodule, a sprinkling of lymphocytes can be seen and the nodules are usually well demarcated from the normal surrounding tissue. This is well shown in a reticulin stain which also shows an abundance of reticulin fibres in contrast to the caseating tuberculous nodule where a dearth of fibres is the pattern. The giant cells can either be of the Langhans type or more usually, of the foreign body type in which numerous nuclei are randomly distributed. Some authorities say caseation never occurs but occasionally fibrinoid necrosis can be demonstrated, while others say that small quantities of caseation may be seen. It is possible that the first view is correct and when true caseation is seen, tuberculosis would be more likely.

The two types of inclusion bodies often associated with this disease are now known to be non-specific, both occurring in giant cells. One is the 'asteroid' of Walbach (1911). This is an acidophilic body which looks like a spider, connected to the rest of the giant cell by numerous legs. The other is the basophilic ovoid or spherical body, which often shows concentric laminations and is nearly always calcified. Schaumann first described this body in 1941, though the Schaumann body may be a calcified asteroid.

These granulomatous nodules may jostle one another, exist cheek-by-jowl or even partially coalesce, but they seldom lose their individuality to form a tuberculoma. Healing is manifested by the process of fibrosis, and

usually the giant cells are the last to be hyalinised.

The histological differential diagnoses are: -

(a) Tuberculosis.
(b) Berylosis.
(c) Lymph node draining a maligant area.
(d) Leprosy.
(e) Silicosis.
(f) Crohn's regional ileitis.

CLINICAL FEATURES

These are so protean that it is best to quote part of the definition of this disease process prepared by the Conference on Sarcoidosis of the National Research Council (quoted by Richer and Clark 1949).

"Clinically, the lesions may be widely disseminated. The tissues most frequently involved are lymph nodes, lungs, skin, eyes and bones, particularly of the extremities.

The clinical course usually is chronic with minimal or no constitutional symptoms; however there may be acute phases characterised by a general reaction with malaise and fever. There may be signs and symptoms referrable to the tissues and organs involved."

Thus, patients may present with fever, malaise, easy fatigability, night sweat and loss of weight. Respiratory symptoms like cough and dyspnoea are common. Haemoptysis is rare. Occular symptoms such as difficulty with vision is a common feature. An infrequent but well known feature is the triad of uveoparotid fever, namely uveitis, swelling of the parotid and other salivary glands, and facial palsy.

Physical examination often discovers features which are highly suggestive of the disease. Peripheral and hilar lymphadenopathy is a common feature. Skin lesions are polymorphic and include erythema nodosum, small discrete nodules over the butterfly area of the face, ears and nose; and finely granular infiltrative plaques — the classical lupus pernio of Besnier. Hepato-splenomegaly and bone lesions, demonstrated radiologically, may be a feature. Arrythmias and neurological manifestations are rare.

DIAGNOSIS

Israel and Sones (1958) who studied 160 cases of sarcoidosis stated: -

"The diagnosis of sarcoidosis requires, in addition to demonstration of consistent histological changes, clinical, laboratory and radiologic evidence, as well as a careful exclusion of the diseases which stimulate sarcoidosis. Most patients with sarcoidosis exhibit a characteristic clinical picture, and in these instances the diagnosis can be made with a high degree of accuracy.

Sarcoidosis is a systemic disease, and in order to establish its presence, systemic involvement must be demonstrated. This may be done by multiple biopsies, but ordinarily, radiologic or clinical evidence of involvement in organs other than the site of biopsy suffices. Thus, an isolated skin lesion which on biopsy shows epithelioid tubercles, may represent a foreign-body reaction; but if in addition, there is histological evidence of similar lesions in a lymph node or the liver or if there is radiological evidence of mediastinal adenopathy or skeletal changes in hands and feet, or if occular changes are observed, a diagnosis of sarcoidosis may be made with assurance."

The participants of the International Conference on Sarcoidosis held in June, 1960, in Washington, D.C. have similar views when they agreed that "the diagnosis should be restricted to patients who have consistent clinical and radiological features together with biopsy evidence of epithelioid tubercles or a positive Kveim Test."

Kveim Test

This is positive in 60% to 80% of patients with sarcoidosis and despite the lack of a standard antigen and occasional difficulties in interpretation, it is a useful diagnostic aid. It is elicited by the intradermal injection of a ten percent suspension of lymph node tissue from a patient with sarcoidosis. In a positive reaction, after a period of six to eight weeks, a nodule develops at the site of the injection, which on biopsy shows the presence of typical sarcoid tissue.

SUMMARY

A case of sarcoidosis is reported in the hope that this seemingly rare disease in Malaysia will be better recognised. A brief review of the literature is made and various points regarding the aetiology, pathology, clinical features and diagnosis are discussed.

We are grateful to Professor E. S. Monteiro for having kindly given us consent to publish the case report.

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