SARCOIDOSIS: A REVIEW OF CASES SEEN AT THE UNIVERSITY HOSPITAL, KUALA LUMPUR

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ABSTRACT

Fourteen cases of sarcoidosis consisting of 7 male and 7 female patients with a mean age of 42.4 years were seen at the University Hospital from 1972 to 1990. There were 10 Indians, 2 Malays, and 2 Chinese. Twelve patients had thoracic involvement. The other common disease manifestations included weight loss, arthralgia, hepatomegaly, erythema nodosum, peripheral lymphadenopathy, and hypercalcaemia. At initial presentation, the disease was in radiographic stage I, II, and III in 8, 3 and one patient respectively. The Kveim test was positive in 7 out of 9 patients. Eight patients required steroid therapy.

Keywords: Kveim test, radiographic stage, sarcoidosis

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INTRODUCTION

Sarcoidosis is rarely encountered in Southeast Asia[1] and its incidence in Malaysia is unknown although it is generally thought to be rare[2]. It is characterized by the presence of non-caseating epithelioid-cell granulomas in one or more organs[3]. In case conforming to a well-recognized pattern, confirmatory histology from one site, either an affected tissue or a Kveim test site, is sufficient to arrive at a diagnosis of sarcoidosis. However, the histological appearance is not always diagnostic and diseases which can give similar histological appearance such as tuberculosis, fungal diseases, local sarcoid reaction to malignancy or lymphoma, have to be excluded.

In a country like Malaysia where the prevalence of tuberculosis is high, there are obvious difficulties with the diagnosis of sarcoidosis, which may resemble the former clinically, radiologically and histopathologically. Tuberculosis has to be excluded, and cases of coexistence of the two conditions have been described[4].

This paper reviews the cases of sarcoidosis seen at the University Hospital, Kuala Lumpur from 1972 to 1990. The clinical features of our cases are compared to cases described in the West.

PATIENTS AND METHODS

The medical records of all patients with a diagnosis of sarcoidosis seen at the University Hospital from 1972 to 1990 were reviewed. The diagnosis was based on the presence of compatible clinical and radiographic features, confirmed histologically, either by biopsy of one or more of the involved tissues and/or by the Kveim test. The presence of non-caseating epithelioid-cell granulomas and the absence of acid-fast bacilli and fungi, on staining and after specific cultures, in the biopsy specimen was considered compatible with the diagnosis.

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Chest X-ray films were classified as stage 0 (normal), stage I (hilar and/or paratracheal lymphadenopathy), stage II (hilar and/or paratracheal lymphadenopathy with pulmonary infiltrates), and stage III (pulmonary infiltrates alone).

The Kveim test was performed with validated test material obtained from Brompton Hospital, London. All patients who had the Kveim test performed, underwent biopsy of the Kveim test site 4 to 6 weeks later regardless of whether a visible reaction was observed or not. A positive test was one which revealed the presence of non-caseating epithelioid-cell granulomas on histological examination.

RESULTS

Fourteen cases of sarcoidosis were diagnosed at the University Hospital from 1972 to 1990 (Table I). The patients consisted of 7 males and 7 females, with a racial breakdown of 10 Indians, 2 Malays and 2 Chinese. During the period of review, ethnic Chinese, Malays and Indians accounted for 41%, 30% and 27% of our total hospital admissions respectively.

Table I - Race and sex distribution

	No. of cases
Malays	2
Chinese	2
Indians	10
Total	14
Males	7
Females	7

The clinical profiles of the patients are summarized in Tables II to IV. Weight loss, joint pain and cough were the most common presenting complaints. The duration of symptoms before presentation ranged from 4 weeks to 2 years with a mean duration of 7.6 months.

The mean age of the patients was 42.4 years with a range of 27 to 72 years. The majority were either in their fourth or fifth decade of life at the time of presentation. Patient 13 first presented at the age of 27 years with clinical and radiographic features of stage II sarcoidosis. She improved spontaneously over a period of about six months. She presented again eleven years later with dyspnoea and features of stage III disease.

A total of 12 patients had thoracic involvement. Dyspnoea was a presenting symptom in 2 patients, both with stage III chest radiographs. Patient 5 was asymptomatic and was referred because of an abnormal chest radiograph which was taken during an annual medical examination.

Evidence of arthritis was present in 4 out of the 6 patients who complained of joint pains. The most commonly affected joints included the ankles, knees, wrists and elbows. All four patients with arthritis also had erythema nodosum. This group constituted half of those with stage I chest radiographs.

Table II - Symptoms and signs at presentation

Weight loss	7
Joint pain	6
Cough	5
Fever	3
Dyspnoea	2
Hepatomegaly	7
Erythema nodosum	5
Peripheral lymph node enlargement	4
Splenomegaly	2
Cranial nerve palsies	2

Table III - Chest radiographs of patients with sarcoidosis

Radiographic stage	Radiographic appearance	No. of patients
0	Normal	2
I	Bilateral hilar lymphadenopathy alone	3
	Paratracheal lymphadenopathy alone	1
	Bilateral hilar and paratracheal lymphadenopathy	4
II	Bilateral hilar lymphadenopathy and pulmonary infiltrates	3
III	Bilateral pulmonary infiltrates without hilar lymphadenopathy	1

Table IV - Investigations

Patient No./Sex/Age	CXR stage	Kveim test	Mantoux test	Serum calcium	Alkaline phosphatase
1/F/60	0	+	-	N	N
2/M/72	0	-	-	Raised	Raised
3/M/30	I	+	-	N	Raised
4/M/33	I	+	-	N	N
5/F/41	I	+	ND	N	N
6/F/49	I	+	-	Raised	N
7/M/46	I	-	-	Raised	Raised
8/M/32	I	ND	-	N	Raised
9/F/32	I	ND	ND	N	ND
10/F/43	I	ND	-	N	N
11/M/38	II	+	-	N	Raised
12/M/40	II	+	+	Raised	N
13/F/27	II/III*	ND	-	N	N
14/F/50	III	ND	ND	N	N

CXR = Chest X-ray N = Normal ND = Not done
* = Refer to text

In addition to erythema nodosum, one patient also developed erythematous maculopapular skin eruptions over his back and chest which lasted for a few weeks. Biopsy of one of the lesions revealed the presence of non-caseating epithelioid granulomas.

Another patient presented with multiple hyperpigmented plaque-like skin lesions on his trunk and lower limbs. Biopsy of the skin lesion revealed evidence of vasculitis.

Hepatomegaly was found in half of our patients but none were jaundiced or symptomatic from their hepatic enlargement. Five patients, including two with hepatomegaly, had elevated serum alkaline phosphatase with levels ranging from 143 to 270 IU/l (Table IV). The other parameters of the liver function test were normal. Four of the patients with hepatomegaly underwent liver biopsy which revealed the presence of non-caseating epithelioid-cell granulomas on histology in all four of them. Palpable splenomegaly was detected in only 2 patients.

The cervical lymph nodes were enlarged in all 4 patients who had peripheral lymphadenopathy. In addition, the axillary nodes were enlarged in 3 patients while one patient had epitrochlear and inguinal node enlargement as well.

Circulating lymphocyte counts of less than 1.5 x 10^9/l were noted in 4 out of the 14 patients. The reduced counts ranged from 0.88 x 10^9/l to 1.35 x 10^9/l.

The Kveim test was performed on 9 patients and positive reaction was seen in 7 patients, one of whom had stage O radiograph, 4 had stage I radiograph, and 2 had stage II radiograph. The negative Kveim response of patient 7 was possibly due to the suppressive effect of steroid treatment he was on because of symptomatic persistent severe hypercalcaemia and multiple cranial nerve palsies at the time the test was performed. Eleven out of 12 patients who had the Mantoux test performed with 2 Tuberculin units of PPD showed negative responses. Patient 12 had a very brisk Mantoux test reaction with 19 mm diameter of induration.

Serum calcium was measured in all the patients. Transiently elevated levels (more than 2.8 mmol/l) were detected in 2 patients while hypercalcaemia which was more persistent in another 2 patients, returned to normal only after steroid therapy. Patient 7 who had serum calcium levels ranging from 2.9 to 3.6 mmol/l actually presented with symptoms due to hypercalcaemia.

Only 7 patients, including the 3 patients with hypercalcaemia, had their 24-hours urinary calcium quantitated. Elevated levels were detected in only 2 patients. While one patient had very persistent hypercalciuria ranging from 9.8 to 16.9 mmol/24 hours (normal: up to 7.5 mmol/1/24 hours) over a two-year period which normalized only after steroid treatment, hypercalciuria was not documented in the other 2 patients with hypercalcaemia. One patient had transient hypercalciuria of 8.64 mmol/24 hours without hypercalcaemia.

Table V - Pulmonary Function Test in Patients with Sarcoidosis

Patient No.	Chest X-ray stage	Vital capacity (% pred)	FEV_1/FVC (%)	Dco (% pred)
1	0	81	87	82
2	I	87	76	ND
3	I	82	80	100
4	I	80	82	100
5	I	81	82	ND
6	I	97	67	ND
7	I	73	69	ND
8	I	85	73	71
9	II	70	90	ND
10	III	40	89	35
11	III	57	90	ND

% pred = % predicted Dco = diffusing capacity
ND = not done for carbon monoxide

Spirometry and lung volumes were measured in 11 patients (Table V). Restrictive changes were seen in 3 patients - the 2 patients with stage III radiographs, one with stage II radiograph. Mild obstructive defects were demonstrated in 2 patients, both having stage I radiographs.

Carbon monoxide diffusing capacity was measured in 5 patients. It was mildly reduced in one patient who had stage I radiograph and was severely reduced in another patient with stage III radiograph.

The indications for steroid therapy, which was in the form of prednisolone, included dyspnoea in patients 12, 13 and 14; marked systemic symptoms in patients 2 and 6; central nervous system involvement in patients 9 and 12; persistent hypercalcaemia in patient 7; and uveitis in patient 11. The response to steroid therapy in seven patients was good. However, the symptoms and radiological changes of patient 12 were unaffected by steroid therapy. Non-steroidal anti-inflammatory drugs were used for symptomatic treatment of arthritis.

Six months after he was diagnosed as having sarcoidosis and while he was still on prednisolone, patient 13 developed a left-sided pleural effusion which was proven to be due to Mycobacterium tuberculosis infection by positive culture of the pleural aspirate. A pleural biopsy revealed the presence of epithelioid granulomas plus acid-fast bacilli. Mantoux test was not repeated this time because he was still on steroid therapy which might have given rise to a false negative response. He responded well to a course of antituberculous treatment while prednisolone therapy was tapered off.

Three patients defaulted follow-up while the average period of follow-up for the rest was 7 years (range 1 to 14 years).

DISCUSSION

Sarcoidosis is rare in Asians except the Japanese who have estimated prevalence and incidence rates of 4 per 100,000 population and 1.3 per 100,000 population respectively[5]. The rarity of sarcoidosis in Southeast Asia and among the Chinese had been noted previously[1,6]. The incidence in Malaysia is unknown although it is thought to be rare[2].

In this series there were equal numbers of Chinese and Malays while the Indians seem to be more susceptible to sarcoidosis as borne out by the fact that despite the ethnic ratio of the admissions to the University Hospital over the period of review the number of cases of sarcoidosis occurring among the Indians was disproportionately high compared to the other two ethnic groups. In 1966 Snelling and Chooi[7] reported only 4 cases of sarcoidosis from Malaysia, all were of Indian ethnic origin. Dutt[8] reported 3 cases of sarcoidosis among the Chinese in Malaysia. The sex ratio of our patients was 1:1. This is in keeping with observations made by many large studies which did not show marked sex predilection for sarcoidosis[9,10]. The male patients in our group presented at an earlier age.

Environmental factors may play an important role in influencing the susceptibility of certain ethnic groups to sarcoidosis.

As it often pursues a silent course, the prevalence of sarcoidosis may be underestimated. There may also be underdiagnosis of sarcoidosis in countries where it is relatively uncommon and where there is a lack of awareness of its existence.

In general, young and middle-aged adults are affected, with the majority of cases developing in patients between the ages of 20 and 40 years[11]. Most of our patients were in their thirties or forties at the time of onset of their disease. Kitamura et al[12] observed that extrathoracic sarcoidosis affected older women more frequently. It is interesting to note that both of our oldest patients had normal chest radiographs which occur in 6 to 14 percent of patients[10,13].

Weight loss was present in half of our patients, especially the older ones. More than one-third had erythema nodosum in contrast to a world-wide study which found it in about 17 per cent of patients[9]. However, the same study also showed that erythema nodosum was common among British patients, being present in about one-third of them as well at presentation. In keeping with observations that erythema nodosum is a feature associated with a benign form of sarcoidosis, 4 of the 5 of our patients with erythema nodosum had stage I chest radiographs at presentation. Also consistent with observations that arthralgia and erythema nodosum are common associations[4], 4 out of 6 of our patients with arthralgia had erythema nodosum.

Although arthralgias are common in sarcoidosis, arthritis is less common, occurring in about 5 per cent of patients[4]. However, almost one-third of our patients had arthritis.

Liver involvement is common in sarcoidosis[14]. Asymptomatic hepatomegaly was found in half of our patients, including 4 who had biopsy evidence of non-caseating epithelioid-cell granulomas in the liver. Elevated alkaline phosphatase levels were seen in 2 patients with hepatomegaly and in 2 without this finding. Maddrey et al[15] found that most patients with liver involvement had increased alkaline phosphatase levels.

While the most common area of lymphadenopathy is the pulmonary hilum, peripheral adenopathy has been reported in up to 25 per cent of patients with sarcoidosis[16]. Two out of 4 of our patients with peripheral lymphadenopathy were actually investigated for a chief complaint of generalized peripheral lymph node enlargement.

Hypercalcaemia is a feature in one out of ten patients with sarcoidosis[17]. Transiently elevated calcium levels are not infrequent, but sustained hypercalcaemia at levels over 2.74 mmol/l (11 mg/dl) is uncommon, occurring in less than 2 per cent of patients. Four of our patients had hypercalcaemia. Two of them had persistently elevated serum calcium which normalized only following steroid therapy. Hypercalciuria, which is due to an increased intestinal absorption of calcium, occurs in up to 50% of patients and is dependent on dietary calcium intake[4]. We detected hypercalciuria in 2 out of the 7 patients who had their 24-hour urinary calcium excretion quantitated.

Among patients with a recent acute onset of sarcoidosis and among those presenting with symptomless bilateral hilar lymphadenopathy, less than half are negative reactors to tuberculin (100 TU)[18]. Although the strength of PPD used for the Mantoux test on our patients was 2 Tuberculin units, 11 out of 12 showed negative response.

Many cases of sarcoidosis and tuberculosis appearing in sequence, and in either order, have been reported[4]. Sometimes there was no obvious interval between the "sarcoid" and the "tuberculous" phases of the illness. Patient 13 illustrates this fact very well.

Four of our patients had lymphopenia while it was seen in 55% of the patients in Baughman's series of 75 patients[19].

A positive Kveim test, done with a validated suspension, is useful as a simple and relatively non-invasive means of supporting a diagnosis of sarcoidosis, when this is compatible with the clinical presentation and other clinical findings. However, the test is not widely available. The Kveim test is positive in 70 - 90% of cases who present with Lofgren's syndrome, ie, fever, erythema nodosum, uveitis, arthralgia, and bilateral hilar lymphadenopathy[20]. However, in patients with purely extrathoracic sarcoidosis, positive response rates have varied from 26% to 50% in the largest studies. The frequency

of positive responses wanes with increasing chronicity of the disease. Sixty-two percent of all subjects with sarcoidosis of less than 2 years' known duration are Kveim positive while in disease of more than 2 years' duration the figure falls to 38%[20].

As corticosteroid treatment suppresses all but the most vigorous positive Kveim responses[20], it is not surprising that the response was negative in patient 13 who was on steroid therapy at the time of the test. Unless it is really essential, steroid treatment should be delayed while awaiting the response of the Kveim test. All responses, whether florid or clinically undetectable, should be biopsied[20].

It is not surprising that 3 out of 5 of our patients who underwent biopsy of the bronchial mucosa had positive results for histology which was compatible with the diagnosis of sarcoidosis, as bronchial wall granuloma is a common pathological finding in sarcoidosis[21-23].

Airflow obstruction in sarcoidosis may be due to the granulomatous process and/or the subsequent fibrosis. There is a lack of a positive relationship between the functional impairment and the radiological staging of the disease[24]. The degree of airway obstruction can be significant even in patients with either stage I disease or a normal chest radiograph.

Corticosteroid treatment does not avert pulmonary fibrosis nor predictably prevents permanent impairment of pulmonary function[25]. The use of corticosteroids is limited to the palliation of disabling symptoms and physiological impairments. Corticosteroids, however, are effective in reducing ocular inflammation, correcting hypercalcaemia and occasionally improving pulmonary function.

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