INTRATHORACIC SARCOIDOSIS

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Sarcoidosis is a systemic disease in which the lungs and intrathoracic lymph nodes are frequently involved. Although the clinical features of patients with sarcoidosis are exceedingly diverse, the majority present with intrathoracic manifestations, detected because of respiratory symptoms or by routine or mass radiography of apparently healthy people. Intrathoracic sarcoidosis is of importance, firstly because it may closely resemble numerous other chest diseases which differ from it greatly in their treatment and prognosis, and secondly because the lung is a site where sarcoidosis may result in serious disability or death.

The Clinical and Radiological Manifestations of Intrathoracic Sarcoidosis

This review of the clinical and radiological manifestations of intrathoracic sarcoidosis is based upon a study of 70 cases seen personally at Brompton Hospital for Diseases of the Chest. Histological confirmation of the diagnosis was obtained in 70 per cent. of these cases. The patients were aged between 18 and 65 years, of whom 70 per cent. were aged between 20 and 40 years. There were rather more females than males.

Study of this group of patients revealed a great variety of intrathoracic disorders associated with sarcoidosis and prolonged observation of individual patients often demonstrated a sequence of different manifestations.

Broadly speaking, the natural history of the disease may be divided, on the basis of radiographic appearances, into three phases:

- (1) Intrathoracic lymph node enlargement.
- (2) Pulmonary shadows.
- (3) Pulmonary fibrosis.

Such an arbitrary division is helpful, since it tends to emphasize certain stages associated with different clinical features and prognosis. Individual patients may present any or all these features during observation. In this series the radiographic appearances are those of the first available chest radiograph and the symptoms those occurring at or before the time of this film unless otherwise stated.

Intrathoracic Lymph Node Enlargement

Radiographic Appearances

Intrathoracic lymph node enlargement of sufficient degree to be obvious in plain chest radiographs is a common feature of intrathoracic sarcoidosis. It occurred in half the patients in the present series (36 patients) (Table 1). Enlargement of the hilar (peri-bronchial) lymph nodes is probably the earliest intrathoracic lesion of sarcoidosis (Scadding, 1950) and may be its only feature. Alternatively, pulmonary shadows may develop and as the shadows progress the hilar nodes often subside so that with long-standing pulmonary lesions enlarged hilar nodes are uncommon. Thus, among 18 cases that had progressed to pulmonary fibrosis, only two showed radiological evidence of hilar node enlargement.

Hilar node enlargement is usually bilateral and remarkably symmetrical (Fig. 1). Occasionally the enlargement is notably asymmetrical, as in four cases, or even unilateral, as in one case among the present 36 cases (Table 1). In a quarter of the cases paratracheal node enlargement was evident (Fig. 1), but in only one case was this present without hilar node enlargement. Enlarged intrathoracic nodes are usually readily evident on the chest radiograph as oval shadows, often well circumscribed, and in almost a quarter of the present series these shadows were gross, being 5 cm. or more in diameter. In case of doubt tomograms at tracheal level are often diagnostic.

Presenting Symptoms and Signs

The presenting symptoms of 20 patients with intrathoracic node enlargement without pulmonary shadowing are detailed in Table 2. Most commonly they were without symptoms and the abnormality was discovered as a result of routine or mass miniature radiography.

Respiratory symptoms are unusual at this stage of the disease and no abnormal physical signs are found in the lungs. Even when hilar node enlargement is gross the bronchi are very rarely significantly narrowed by compression (one case only this series), although bronchoscopic biopsy of

TABLE 1.—RADIOLOGICAL FEATURES OF INTRATHORACIC SARCOIDOSIS
INTRATHORACIC LYMPH NODE ENLARGEMENT IN 36 PATIENTS

Hilar node enlargement	35
Bilateral symmetrical	30
Bilateral asymmetrical	4
Apparently unilateral	1
Para-tracheal node enlargement	9
Nodes 5 cm. or more in diameter	8

PULMONARY SHADOWING WITHOUT RADIOLOGICAL EVIDENCE OF FIBROSIS IN 40 PATIENTS

Type of Shadows		Distribution	
Mottling:		Bilateral middle zone	14
Micronodular	5	Bilateral generalized	13
Nodular	20	Bilateral upper and middle zone	7
Coarse nodular	5	Bilateral upper zones	2
Reticulo-nodular	7	Unilateral	4
Cloudy shadows	3		
	40		40
Hilar node enlargement	25	Perihilar streaking	6

PULMONARY FIBROSIS IN 18 PATIENTS

Evidence for Fibrosis		Types of Shadows	
Hilar displacement	12	Dense middle zone shadows with or without other shadows	10
Displaced fissures	3	Reticular or reticulo-nodular	9
Tracheal shift	2	Mottling	8
Cardiac shift	1	Hilar node enlargement	2
		Hypertranslucency suggesting emphysema	8
		Ring shadows	6

FIG. 1.—Bilateral hilar node and right paratracheal node enlargement.

normal-looking mucosa may reveal microscopic involvement (Kalbian, 1957). Occasionally hilar node enlargement is associated with iridocyclitis, erythema nodosum or rheumatism. The syndrome of erythema nodosum, rheumatism, bilateral hilar

TABLE 2.—PRESENTING SYMPTOMS IN 70 SARCOIDOSIS PATIENTS

Symptoms	Hilar Node	Pulmonary Shadows	Pulmonary Fibrosis
Respiratory symptoms	4	15	16
Asymptomatic (routine or M.M. film)	9	5	2
Erythema nodosum or rheumatism	3	5	0
Iridocyclitis	4	2	0
Lassitude	0	4	0
Skin lesion	0	1	0
Total	70	32	18

node enlargement with or without pulmonary shadows, and absent or low tuberculin sensitivity, is most commonly associated with sarcoidosis (James, Thomson and Willcox, 1956) and was a presenting feature in eight of 70 patients.

Pulmonary Shadows

Radiographic Appearances

A great variety of radiographic shadows may occur in pulmonary sarcoidosis, but four principal types may be recognized:

1. Mottling (Fig. 2). These shadows have been subdivided into (a) micro-nodular, rounded shadows less than 1 mm. in diameter; (b) nodular

FIG. 2.—Pulmonary mottling.

FIG. 3.—Cloudy shadows in the lungs.

1 to 3 mm. in diameter; and (c) coarse nodular more than 3 mm. in diameter.

2. Reticular (net-like) or reticulo-nodular shadows.

3. Cloudy shadows, either homogeneous (Fig. 3) or consisting of conglomerate nodular or reticular shadows.

4. Peri-hilar streaky shadows radiating from hilum into the lung fields.

In this series there were 40 patients whose chest radiographs showed pulmonary shadows, but no radiological evidence of fibrosis. In 32 this was evident in the first available radiograph and in eight with hilar node enlargement it developed whilst under observation.

The principal type of shadow evident in each of these radiographs is detailed in Table 1.

Commonly the shadows consisted of mottling, which was four times more common than reticular or reticulo-nodular shadows. The mottling was usually nodular, although both micro-nodular and coarse mottling occurred quite frequently. Cloudy shadows occurred (Fig. 3) as the only shadowing in the lung in three patients but occurred in association with other shadows in six.

The shadows were usually distributed in the middle zones of both lungs or uniformly through all zones of both lungs, but in about one-fifth the upper zones of both lungs were involved either alone or with the middle zones also. In one-tenth the shadowing was unilateral. Peri-hilar streaking was an additional feature in some films.

Pathology

The pathological basis of these radiological features consists principally of miliary sarcoid granuloma in the interstitial tissue of the lung, usually numerous and widely distributed, with a tendency to invade peri-bronchial and peri-hilar areas. Intervening lung is normal or slightly emphysematous (Longcope and Freiman, 1952).

Physiology

Some patients subjected to physiological investigation showed evidence of alveolo-capillary block. This was characterized by normal maximum ventilatory capacity, normal or slightly reduced total lung capacity with normal subdivisions, hyperventilation at rest and on exercise, normal or slightly reduced arterial oxygen at rest, but desaturation on exercise, increased alveolo-capillary oxygen gradient, and impaired pulmonary carbon monoxide diffusion. Some patients had evidence of emphysema with increased residual capacity and impaired gaseous mixing in the lung.

Symptoms and Signs

The symptoms of 32 patients presenting with pulmonary shadows are detailed in Table 2.

Cough, dyspnoea and rarely chest pain were presenting features in about half, the rest suffered from erythema nodosum or rheumatism, lassitude, iridocyclitis, skin lesions or were detected by routine or mass radiography. Physical signs in the lungs were conspicuous by their absence.

FIG. 4.—Pulmonary fibrosis.

Pulmonary Fibrosis

Radiological Appearances

In 18 patients the first available radiograph suggested pulmonary fibrosis (Table 1). Displacement of hilar vessels on one or both sides was the usual evidence of fibrosis, but in other cases displacement of the trachea, heart or fissures was accepted as suggestive. Such findings indicated irreversible changes and no case with these findings showed complete radiological or symptomatic resolution.

The most characteristic appearance at this stage was widespread, ill-demarcated homogeneous or reticular shadows in the middle zones (Fig. 4). Cloudy shadows were also frequent, but reticulo-nodular shadows were more common than nodular shadows and micro-nodular shadows occurred only once in contrast to the findings in the previous group without fibrosis. Apical or basal hypertranslucency suggesting emphysema was common. Ring shadows occurred in six, clinical and radiological evidence suggesting that these were due to emphysematous bullae in two, dilated bronchus in one, one followed a probable lung abscess, and one was a cavity in an area of fibrosis possibly due to ischaemic necrosis, as suggested by Scadding and Lennox (1950). One apical cyst became filled with a mass of *Aspergillus fumigatus* mycelium.

Pleural shadows occurred only once among 70 patients and spontaneous pneumothorax only twice.

Bronchographic abnormalities occurring in fibrotic sarcoidosis include 'concertina' dilatation of the smaller bronchi and crowding and displace-

ment of bronchi as in other forms of pulmonary fibrosis. Rarely multiple bronchial stenoses occur (Citron and Scadding, 1957a). These have a predilection for the level of origins of the segmental bronchi which may show post-stenotic dilatation. Less often the main bronchi are also narrowed.

Pathology

Miliary granulomata fibrose and confluence of such lesions leads to replacement of normal lung structure by fibrous tissue. Compensatory emphysema and bronchial dilatation and stenosis may occur.

Physiology

Most patients with these radiological appearances show physiological evidence of fibrosis with much impaired maximum ventilatory capacity and low total lung capacity and show also evidence of emphysema, including increased residual capacity and impaired gaseous mixing in the lungs.

Symptoms and Signs

The great majority of patients at this stage of the disease complain of respiratory symptoms (Table 2). Effort dyspnoea may be severe and some patients are respiratory cripples. They are particularly liable to intercurrent respiratory infections. Patients with multiple bronchial stenoses characteristically have severe dyspnoea with stridor and recurrent pulmonary infections behind the strictures.

Physical signs in the lungs usually consist of diffuse rhonchi and rales. Finger clubbing is exceptional. Pulmonary heart disease secondary to extensive pulmonary fibrosis may occur. Much less commonly heart block, cardiac arrhythmias, congestive failure or sudden death is attributable to direct invasion of the myocardium by sarcoidosis (Longcope and Freiman, 1952).

Diagnosis and Differential Diagnosis

The detection of extrathoracic lesions of sarcoidosis, such as skin rash, lymphadenopathy, splenomegaly, eye and bone lesions is of the greatest help in support of the diagnosis of intrathoracic sarcoidosis and may provide material for histological confirmation. Such confirmation was obtained from biopsy of liver in 19, lymph node in 14, skin in nine, bronchial mucosa in four, lung in two and conjunctiva in one of the present series.

Deficiency of tuberculin type skin reactions (Citron, 1957), positive Kveim skin test (James and Thomson, 1955), hyperglobulinaemia and hypercalcaemia (Citron, 1955) also contribute evidence for the diagnosis.

The differential diagnosis of pulmonary sarcoidosis is wide. Scadding (1952) has listed 73

causes of pulmonary shadows which might resemble sarcoidosis.

The following conditions are those most likely to be confused with pulmonary sarcoidosis:

Caseating Pulmonary Tuberculosis

Features which are common in this condition but uncommon in sarcoidosis include high tuberculin sensitivity, apical distribution of shadows, unilateral hilar node enlargement and good response to anti-tuberculous drugs. Caseation in biopsy specimens excludes sarcoidosis as defined histologically (Scadding, 1950), but the finding of tubercle bacilli does not, nor does calcification in lung or hilar nodes. Such calcification, in fact, was evident in plain radiographs in 20 per cent. of the present series.

In some cases of very indolent tuberculosis with low tuberculin sensitivity the distinction from sarcoidosis is largely a verbal one (Scadding, 1956a). Difficulty is increased because it is well recognized that patients with sarcoidosis may develop features of caseating tuberculosis.

Dust Diseases of the Lung

These are excluded by a comprehensive occupational history. The clinical and pathological features of chronic beryllium poisoning may closely resemble those of sarcoidosis. However, the ocular and cystic bone changes of sarcoidosis and hilar node enlargement without pulmonary shadows have not been described in beryllium disease. Sometimes differentiation can only be made by the detection of beryllium in the granulomata by chemical or spectrographic methods (Hardy, 1956).

Neoplastic Diseases of the Lung

Lymphangitis carcinomatosa differs from sarcoidosis in the very rapid progression of severe dyspnoea.

Patients with Hodgkin's disease or leukaemia have usually more constitutional disturbance than patients with sarcoidosis and specific changes are found in examination of lymph nodes or blood.

Lung Shadows Associated with Cardiovascular Diseases

These include pulmonary haemosiderosis and pulmonary oedema and are distinguished from sarcoidosis by the presence of cardiovascular abnormalities.

Diffuse Interstitial Fibrosis of the Lungs of Unknown Cause

The acute form of this condition (Hamman-Rich disease) differs from sarcoidosis in the very rapid progression of dyspnoea and chronic inter-

stitial fibrosis by the frequency of marked finger clubbing and the presence of coarse rales throughout the lungs.

Collagen Diseases of the Lung

The distinction is usually easy when pulmonary changes are associated with the renal, cardiovascular, dermal, joint or neurological involvement in the collagen diseases. The pulmonary manifestations of polyarteritis nodosa may be accompanied by blood eosinophilia which is exceptional in sarcoidosis.

Prognosis

The course of intrathoracic sarcoidosis is notoriously variable and unpredictable. Lung lesions may resolve within a few months, but sometimes relentless progression to extensive fibrosis occurs in a few years, or may take a decade or more with ultimate death from lung or heart failure. Scadding (1956b) has described 102 cases of intrathoracic sarcoidosis observed for two to 14 years. Of 16 patients first seen with enlarged hilar nodes, six developed diffuse shadows in the lungs, but 15 eventually had normal chest radiographs and all became symptom free.

Among 32 patients with pulmonary shadowing associated with or preceded by hilar node enlargement, 18 resolved completely and are well and two still had radiographic abnormality but were symptom free, seven had mild respiratory symptoms, one severe symptoms and three died of sarcoidosis. Among 53 patients who had pulmonary shadowing but no record of previous hilar node enlargement, only 14 were well with normal radiographs, four had radiographic abnormalities but no symptoms, 22 had mild, 10 severe symptoms, and two had died of sarcoidosis. Those cases without hilar node enlargement may represent a group whose sarcoidosis is of longer standing and therefore have a worse prognosis than those with hilar node enlargement. Certainly hilar node enlargement is exceptional in the presence of established pulmonary fibrosis (see above).

Treatment of Pulmonary Sarcoidosis

Cortisone and its derivatives and corticotrophin are the drugs which are of most value in the treatment of pulmonary sarcoidosis. Unfortunately, short-term treatment offers little hope of permanent improvement and continuous treatment for long periods is usually necessary (Hoyle, Dawson and Mather, 1955) and is associated with all the well-known dangers of prolonged corticosteroid therapy. Anti-tuberculosis drugs appear of limited value, except where pulmonary sarcoidosis has been present a short time only (Hoyle, Dawson and Mather, 1955).

The natural history of pulmonary sarcoidosis is so variable that it is difficult to select patients in whom treatment will in the long run favourably influence the course of their disease. To treat all patients with pulmonary sarcoidosis with corticosteroids is unjustifiable, since it would subject unnecessarily many patients, who might otherwise have remained well, to the hazards of prolonged corticosteroid therapy. Cases with hilar node enlargement without pulmonary shadows should not be given corticosteroids, because spontaneous resolution is the rule. Cases of pulmonary sarcoidosis with mild respiratory symptoms and judged to be of recent onset can safely be observed for one year, during which there is a good chance of spontaneous resolution. During this time anti-tuberculosis drugs (i.e. isonazid and PAS) may be given. If in this time there has been no improvement corticosteroid treatment should be considered. Prednisolone or prednisone, 20 to 30 mg. daily, may produce radiological improvement and after six or eight weeks the dose may be reduced to the least dose sufficient to maintain the radiological and symptomatic improvement. Corticosteroids should be continued as long as they are judged to be exerting a favourable influence on the disease; that is, until withdrawal of these drugs can be accomplished without symptomatic or radiological relapse. It is desirable to cover corticosteroid therapy with anti-tuberculosis drugs because many cases of sarcoidosis appear to be of tuberculous origin (Scadding, 1956b; Citron and Scadding, 1957b).

Cases of sarcoidosis with established pulmonary fibrosis, marked respiratory symptoms or physiological evidence of fibrosis or emphysema usually merit steroid therapy without preliminary prolonged observation. Treatment at this stage produces limited radiological improvement, but further lung damage may be prevented and symptomatic relief is often marked. There is no evidence that rest, or a sanatorium regime, influences sarcoidosis and patients may be permitted to lead as normal a life as their disability will allow.

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