

Sarcoidosis: the clinical problem

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Summary: This paper reviews the clinical manifestations of acute and chronic sarcoidosis. The indications for measuring serum angiotensin converting enzyme and for performing pulmonary function tests, bronchiolo-alveolar lavage and gallium scans are discussed and the modern indications for performing a Kveim Siltzbach test are also considered. The main treatment available for patients with sarcoidosis is systemic steroids and the indications in the various systems for using these drugs are discussed.

Introduction

Sarcoidosis occurs in 19 out of every 100,000 white people in the United Kingdom. However, in areas of high immigrant population this figure may be increased, as the prevalence of the condition in West Indian immigrants is 40 per 100,000, whilst in the Irish living in London the figure has been reported to be as high as 160 per 100,000.¹ Asian immigrants are less commonly affected, but sarcoidosis is being increasingly found in this group as well, though figures are not available for the prevalence. Indeed, the above quoted figures date from the days when mass radiography was available in the United Kingdom and may no longer be valid. Sarcoidosis most commonly presents between the age of 20 and 40 years, though any age may be affected. There is no predilection for either sex, but most reported series include a slightly higher number of female patients.

Acute sarcoidosis

As recently as 1946, Löfgren² drew attention to the syndrome of erythema nodosum, arthralgia, bilateral hilar lymphadenopathy and occasionally acute anterior uveitis. Prior to this, sarcoidosis had been considered a chronic disabling condition, but Löfgren was able to identify this clinical entity as a form of sarcoidosis and establish its good prognosis.

Erythema nodosum

This skin rash presents acutely with red tender spots on the shins which gradually fade to bruises.

It most commonly occurs in females and there is often a constitutional upset preceding the rash with flitting joint pains, fever and sweating. The rash may occasionally extend to the thighs or forearms and very rarely to the upper arms and neck. It does not affect the posterior aspect of the lower limbs. Painful red nodules at this site should be considered to have a different differential diagnosis including superficial vein thrombophlebitis and tuberculous erythema induratum.

Treatment is rarely required for erythema nodosum itself. The painful arthralgia usually responds to non-steroidal anti-inflammatory agents, though occasionally patients are so unwell that a course of steroids is appropriate. The rash always disappears with oral prednisolone, but may recur when the drug is stopped.

Erythema nodosum conveys a good prognosis to patients with sarcoidosis, but, nevertheless, 12% of patients presenting this rash will run a chronic course.³

Other acute skin lesions

In acute sarcoidosis, old scars, e.g., appendicectomy, knee lacerations or venepuncture sites, may flare up and be mistaken for keloid formation. Biopsy reveals sarcoid tissue. Rarely a maculopapular rash may be an acute manifestation of sarcoidosis, but most other skin lesions are found when chronic features are present elsewhere.

Acute anterior uveitis

A painful red eye linked with erythema nodosum is a strong indication of sarcoidosis. Examination will reveal the characteristic circumciliary injection of

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uveal tract inflammation. Slit lamp ophthalmological examination will reveal keratic (mutton fat) precipitates in the anterior chamber. Treatment includes topical steroids and homatropine eyedrops which should usually be supervised by an ophthalmologist.

Peripheral lymphadenopathy

Peripheral lymph node enlargement has been reported in up to a quarter of all patients with sarcoidosis. No particular group of nodes are prominent and the nodes themselves are usually discrete and mobile. It is very unusual for the nodes themselves to persist.

Radiological appearances

Bilateral hilar lymphadenopathy (BHL: Stage I) is almost always due to sarcoidosis, but occasional patients are seen with lymphomas and therefore the diagnosis cannot be assumed from the radiographic appearance. There are often no associated respiratory symptoms, but occasionally there may be non-specific cough or vague chest pain and rarely dyspnoea. Patients presenting with BHL alone have a good prognosis and three-fifths of the radiographs will eventually return to normal.³

Chronic sarcoidosis

Skin lesions

Chronic persistent violaceous, brown or erythematous skin plaques are the hallmark of chronic sarcoidosis. They usually present insidiously and the patient may admit to having noticed them some years prior to seeking medical attention. If they are found on the nose, the cheeks or the ears, then the condition is often termed lupus pernio. There may be a single purple red digit, which may or may not be associated with underlying bone sarcoidosis. No matter where these lesions are found, they will persist for years and although they may shrink and become less obvious after steroid therapy, they will rarely disappear completely. There will usually be manifestations of chronic sarcoidosis in other bodily systems. Subcutaneous nodules are sometimes noted and in black patients this may be associated with loss of pigment of the overlying skin.

Chronic relapsing uveitis

Patients with a chronic or intermittently red eye and less pain than experienced with acute uveitis

may be found to have inflammation of the anterior uveal tract before or after a diagnosis of systemic sarcoidosis is made. In chronic anterior uveitis, the pupil may become deformed and keratic precipitates may be more obvious. Topical steroids and miotics are mandatory and systemic steroids may be necessary to preserve sight. Posterior uveitis is a relatively rare manifestation of ocular sarcoidosis but may be visible after dilatation of the pupil as sheathing of the vessels, candle grease exudates, occasional haemorrhages and sometimes papilloedema.

Chest radiographic abnormalities

Over 90% of patients with sarcoidosis have involvement of the respiratory tract. In a worldwide review of sarcoidosis, 92% of 3676 patients had abnormalities on their chest radiograph at presentation. Fifty-one percent had a Stage I chest X-ray, 29% Stage II (BHL plus pulmonary infiltration) and 12% Stage III (pulmonary infiltration alone). Overall, 65% of Stage I chest X-ray eventually resolved, 49% of Stage II and 20% only of Stage III chest radiographic abnormalities achieved resolution.⁴

Less common manifestations of sarcoidosis

Hepatosplenomegaly

Splenomegaly occurred in 12% of patients and hepatomegaly in 10%, while hepato-splenomegaly was present in 5% of patients at a specialized sarcoidosis clinic.³ Although leucopenia was frequent, hypersplenism was noted only once. This patient was one of the two patients in the above series who were known to have liver fibrosis and portal hypertension secondary to sarcoidosis. Both hepatomegaly and splenomegaly were linked to remission of the disease in about a third of patients.

Upper respiratory tract sarcoidosis

Involvement of the mucosa of the upper respiratory tract is uncommon, but linked with lupus pernio. Within two years of presentation with nasal symptoms, 50% of patients will develop disfiguring lupus pernio when sarcoid granulomas are found in the nasal mucosa. Very rarely laryngeal or pharyngeal involvement may be associated. Both lupus pernio and sarcoidosis of the upper respiratory tract are manifestations of chronic fibrotic sarcoidosis and reflect this chronicity elsewhere. Resolution of intrathoracic involvement occurred in about one quarter of patients with sarcoidosis of the upper respiratory tract and remission of the disease within two years occurred in only about 15% of patients.³

Central nervous system

About one tenth of patients with sarcoidosis will have involvement of the central nervous system. The commonest lesion is a lower motor neurone facial palsy and sarcoidosis should always be considered in any patient who has recurrent or bilateral 'Bell's' palsy. These facial palsies usually recover spontaneously leaving few sequelae. Other lesions include a mononeuritis multiplex, which may involve other cranial nerves, or space-occupying granulation tissue in the brain or brain stem. These may cause permanent neurological disability and have a poor prognosis. Myopathy and peripheral neuropathy have also been described.

Salivary and lacrimal glands

Parotid swelling is reported in 6% of patients with sarcoidosis and lacrimal swelling in 3%. This may be accompanied by dry eyes (keratoconjunctivitis sicca) and dry mouth (xerostomia), though this sicca syndrome may occur separately without glandular enlargement.

Bone

Bone abnormalities reflect chronic sarcoidosis and occur in 4% of patients. It is most characteristically associated with chronic skin lesions or sarcoidosis of the upper respiratory tract and classically presents with bone cysts at the distal ends of the phalanges, carpal or tarsal bones. Other abnormalities have also been reported. Although this is usually a radiological abnormality, 50% of patients with bone digital sarcoidosis will complain of pain, swelling and stiffness of the affected digits.

Kidney

Although hypercalciuria may be found in 40% of patients when it is sought, nephrocalcinosis with residual irreversible renal impairment is rare, occurring in only 1% of patients.³

Heart

Myocardial sarcoidosis is rarely diagnosed in life because the usual presentation is of sudden death due to a cardiac dysrhythmia.⁵ Cor pulmonale may complicate chronic pulmonary fibrosis and then has a poor prognosis, as it is the major cause of death due to sarcoidosis.⁶

Investigations

Calcium metabolism

Hypercalcaemia has been noted in between 3%–

28% of a series of patients with sarcoidosis with a mean of 11%.⁴ A patient may return from a holiday in the sun complaining of polyuria, polydipsia, malaise and perhaps constipation. If there is no glycosuria, then the next possibility is hypercalcaemia due to vitamin D hypersensitivity in sarcoidosis. Patients with sarcoidosis who plan a holiday in the sun are well advised to use a modern high factor UV barrier cream in order to prevent synthesis of vitamin D in the skin. Hypercalciuria has been found in up to 40% of patients when it is sought, but is asymptomatic and rarely leads to nephrocalcinosis (*vide supra*).

Serum angiotensin converting enzyme

Patients with active sarcoidosis have been shown to have elevated values of serum angiotensin converting enzyme (SACE).⁷ The anticipation that this biochemical assay could be used as a definitive test for sarcoidosis has not been realised, for in published series less than half the patients with adequate confirmed sarcoidosis have elevated values of SACE.⁸ The current consensus view on the place of SACE in the management of patients with sarcoidosis is that serial measurement of SACE may prove helpful in assessing disease activity. However, steroid drugs in a dosage equivalent to 20 mg of prednisolone reduce serum SACE activity, but do not invariably suppress activity to within the normal range. SACE is not a diagnostically specific test for sarcoidosis, as occasional false positives are found in patients with pulmonary tuberculosis and Hodgkin's disease.

Other blood tests

Haemoglobin may be high (secondary polycythaemia due to hypoxia) or low (haemolysis or hypersplenism), but is usually normal. The white cell count is usually low normal with a reduced total number of lymphocytes. With special techniques it is seen that this reduction is largely in the T lymphocytes. A mild eosinophilia is sometimes seen, particularly in Black patients.

Hyperglobulinaemia is found in up to three quarters of sarcoidosis patients, but this is a non-specific reaction, including all classes of immunoglobulins and antibodies to various viruses and bacteria. None of these antibodies has proved to be of diagnostic significance. Small rises in hepatocellular enzymes are commonly found, reflecting sarcoid granulomas in the liver. Bilirubin elevation is uncommon.

Skin tests

Tuberculin test (Mantoux or Heaf test) is negative

in two-thirds of patients with sarcoidosis in this country. This is not usually of great diagnostic help nowadays, as tuberculosis is so much less common than previously. There are also many other conditions such as lymphomas which are associated with negative tuberculin skin tests, as well as negative skin tests to a variety of other antigens when tested for delayed hypersensitivity.

Kveim Siltzbach test is still useful in selected patients where a histological confirmation of the diagnosis of sarcoidosis is being sought and where this is not urgent, as this must include a biopsy of the site of injection some 4–6 weeks subsequent to the date of injection. The clinical indications for this might be in patients who presented with uveitis, liver granulomas, cerebral or muscle granulomas or other isolated findings suggestive of sarcoidosis without evidence of multisystem involvement. Now a days most chest physicians will proceed to bronchoscopy to obtain histology from lung or bronchial tissue at an earlier stage, often associated with bronchoalveolar lavage (*vide infra*).

Pulmonary function tests Pulmonary function abnormalities do not correlate well with radiographic appearances. However, they are more common in Stage III than in Stage II or, in turn, Stage I patients. The classical abnormality is a restrictive defect with a low gas transfer, as found in any fibrotic lung disease. However, air flow obstruction is being increasingly recognized, even in patients who are non-smokers. This includes both small airways, medium sized airways and large central airways.⁹

Bronchioloalveolar lavage

Bronchioloalveolar lavage (BAL) is becoming increasingly a routine investigation of patients with sarcoidosis. Like SACE, although it is not necessarily a useful diagnostic test, it may be a useful guide to disease activity when increased numbers and percentages of activated T lymphocytes are found in the BAL.¹⁰ BAL is quite different in patients with fibrosing alveolitis who tend to have predominantly neutrophils in the washings. Many other investigations have been reported on BAL in patients with sarcoidosis, but these, to a large extent, should be regarded as research procedures, whereas a simple white cell differential count is possible in most district general hospitals. It is clinically justified, as bronchoscopy is often performed nowadays to obtain histology.

Gallium scans

Gallium scanning of the lung is also regarded as a

useful indicator of disease activity. Unfortunately, on account of the radio-activity involved, it is rarely justified to do serial scans.

Treatment

The sheet anchor of treatment in sarcoidosis patients is still systemic steroids. It is rarely necessary to exceed a dose equivalent to 20 mg of prednisolone daily. Satisfactory control of symptoms is usually obtained within 4 weeks, though total suppression of granuloma activity may not occur for some time longer. The dose is, however, usually reduced after the 4 week period, though a small dose may need to be continued for many months.

Indications for treatment

Respiratory Dyspnoea is an absolute indication for treatment. There is controversy over treatment of radiological and physiological abnormalities, but in general a worsening pulmonary infiltrate or deteriorating lung function tests are regarded as indications for starting treatment or for increasing the dose of steroids. Elevated angiotensin converting enzyme, elevated lymphocytes in the BAL or an abnormal gallium scan are not, in themselves, an indication for treatment, though they may give some help as to whether or not treatment is adequate if serial tests are being performed (as suggested above, this is hardly indicated for gallium scans).

Extrathoracic Anterior uveitis will generally respond to topical steroids, but if it does not or in the presence of posterior uveitis, then systemic steroids should be initiated.

Chronic skin lesions in themselves do not require treatment, but the cosmetic disaster of lupus pernio in the young woman certainly does. Plastic surgery and ear, nose and throat repair operations should be avoided in these circumstances.

Myocardial or central nervous system involvement usually constitute an absolute indication for treatment. Abnormal liver function tests are not an indication to start treatment, but when portal hypertension or hypersplenism develops, then it is usually appropriate. Manifestations of sarcoidosis in bone, joints or salivary glands may sometimes need treatment, depending on the degree of dysfunction and discomfort caused to the patient.

Other drugs

Chloroquine may occasionally be beneficial in patients with fibrotic sarcoidosis, but regular ophthalmological checks for ocular toxicity are

required. Occasionally some benefit is found from azathioprine or cyclophosphamide when it is added

to steroid therapy. However, any affect from any of these drugs is usually difficult to document.

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