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Sarcoidosis

Recognition and Treatment Guidelines

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Summary

Sarcoidosis is a systemic disorder of unknown aetiology characterised by non-caseating granulomas leading principally to bilateral hilar lymphadenopathies, pulmonary infiltration and skin and eye lesions. Sarcoidosis may involve other organs, including peripheral lymph nodes, liver, spleen, nervous and musculoskeletal systems, heart, ear, nose and kidney. Although the clinical involvement of liver and heart is relatively uncommon, hepatic and cardiac granulomas are present at autopsy in about 70 to 80% and 25 to 50%, respectively, of patients with this disease.

The diagnosis of sarcoidosis includes compatible clinical and/or radiological presentations and histological evidence of noninfectious and noncaseating epitheloid cell granulomas in the absence of other identifiable agents responsible for such histological lesions. Disease course is variable and usually characterised

by frequent remissions, but it may become progressive and chronic in a small percentage of patients.

The optimal treatment of sarcoidosis remains poorly defined. In patients with progressive pulmonary dysfunction as well as in those with severe extrapulmonary localisations, systemic corticosteroids usually represent the first approach, limited by long term toxicity and frequent relapses after treatment interruption.

In the presence of refractory or corticosteroid-dependent forms of the disease, antimalarial drugs or low dosage methotrexate may be used with prolonged benefit. The indications for immunosuppressive agents such as azathioprine, chlorambucil, cyclophosphamide and cyclosporin are uncommon and limited because of potentially serious adverse effects and lack of information on their long term efficacy.

In the case of ocular and limited cutaneous manifestations, local corticosteroid therapy may be useful.

1. Aetiopathogenesis

Sarcoidosis is a granulomatous disorder mediated by an intense cellular immune response localised at the sites of disease activity. The initial pulmonary lesion might be an inflammatory alveolar process (alveolitis), which is essential to the development of the granulomas.[1] Unknown specific antigens, partially degraded by macrophages and presented to T helper (CD4) lymphocytes, trigger an immune response. A probable imbalance between the two CD4 subpopulations (T helper 1 and 2) is responsible for activation and proliferation of lymphocytes. Subsequently, this lymphocytic activation leads to recruitment and proliferation of monocytes-macrophages, and differentiation into epitheloid cells. In all these steps, not only direct intercellular contact but the production of many cytokines (interleukin-1β, interleukin-2, interferon-γ, tumour necrosis factor-α, granulocyte-macrophage colony-stimulating factor, transforming growth factor-β, monocyte chemotactic factors, migration inhibitory factors) are also implicated.[2]

Among potential causes for the initial inflammation, infectious agents have long been suspected, but the question remains unsettled. In particular, the role of *Mycobacterium tuberculosis* in this disease, at least in some cases, has been suggested[3] but not confirmed in a recent study.[4] Genetic and environmental factors might also be implicated in sarcoidosis.

2. Clinical and Radiological Features

Sarcoidosis affects men and women equally. It appears to be more prevalent in certain populations (e.g. Scandinavian, Irish) but more aggressive in African-Americans and West Indians. Although this disease most commonly presents during the third or fourth decade, sarcoidosis also occurs in children and the elderly. Clinical abnormalities, as shown in table I, are highly variable but involve mediastinal and pulmonary localisations in about 90% of cases.

2.1 Endothoracic Manifestations and Imaging

Detection of x-ray abnormalities in an asymptomatic patient is by far the most common presentation of sarcoidosis. Clinical pulmonary manifestations include cough, dyspnoea and chest pain, and may occasionally be associated with symptoms such as malaise, fever and bodyweight loss. The combination of isolated hilar adenopathy, arthralgia and erythema nodosum (Lofgren's syndrome) usually indicates a favourable prognosis.

The prognosis of endothoracic sarcoidosis depends principally on the x-ray type encountered, as classified into the 4 groups shown in table II. Un-

Table I. Clinical manifestations of sarcoidosis in order of frequency

Lung and mediastinum (see table II)
Skin (erythema nodosum, lupus pernio, nodules, plaques, ulcers)
Eye (lachrymal glands, conjunctiva, uveal tract)
Spleen and lymph nodes
Musculoskeletal system (muscles, peripheral bone, joints)
Nervous system (meninges, brain, cranial and peripheral nerves)
Parotid glands
Heart
Kidney

usual chest radiological images include unilateral presentation, atelectasia, bronchiectasia, pulmonary cavity or consolidation and pleurisy. High resolution computed tomography (CT) examination allows better visualisation and localisation of radiographic abnormalities and may be useful for differentiation between active (reversible) and fibrous (irreversible) pulmonary lesions.[5] Pulmonary function tests, including vital capacity and diffusing capacity, are essential to evaluate the severity of the pulmonary lesions and to measure the therapeutic response.[6]

2.2 Skin Manifestations

The cutaneous manifestations of sarcoidosis are frequently the initial symptoms. They are found in 10 to 35% of cases and are present at various localisations (face, hands, feet, nape of the neck) as well as in various presentations (small or large nodules, scar sarcoidosis, plaques, lupus pernio, infiltrate or hypodermic lesions). These cutaneous lesions are easily accessible to biopsy, and the majority of them show specific histological features, characterised by a noncaseating epitheloid gigantocellular granuloma. However, erythema nodosum and more rarely other aspecific lesions such as vasculitis and erythema polymorph may be observed.

2.3 Ocular Manifestations

The ocular manifestations of sarcoidosis are varied and aspecific. They occur in approximately 30% of cases. These granuloma lesions can involve all the structures of the eye itself but also the surrounding tissues and optic nerve. Conjunctival or lacrimal gland infiltrations are the most common lesions, and remain benign. Uveitis is present in about 20% of all cases and may evolve to a chronic condition. Among all cases of ocular sarcoidosis, posterior uveitis, frequently associated with central nervous system involvement, is the major cause of visual morbidity. A systematic ocular investigation is thus necessary in all patients presenting with sarcoidosis.

2.4 Musculoskeletal Manifestations

Asymptomatic muscle lesions may affect 50 to 80% of patients with sarcoidosis; only 1.4 to 2.3% of patients experience either chronic progressive myopathy, palpable nodules or, rarely, acute myositis. Although a usually self-limiting acute polyarthritis affects 10 to 20% of patients with early disease, the main joint lesion observed in persisting sarcoidosis is a rare (0.2%) synovitis of joints and tendon sheaths leading to a chronic polyarthritis with potential deformations and irreversible damage. Bone lesions, asymptomatic in half of the cases, are observed in an average 5% of patients (range 1 to 13%), and consist of an altered trabecular pattern, minute cortical defects and cystic lesions whose preferential localisations in middle and distal phalanges can underlie a clinical polydactylitis.

2.5 Neurological Manifestations

Nervous system involvement is rare but severe with multiple localisations including, in decreasing frequency, meninges, brain and spinal cord, cranial nerves (facial) and peripheral nervous system. Analysis of cerebrospinal fluid shows an in-

Table II. Chest radiographic types of sarcoidosis and their corresponding spontaneous resolution after 5 years (%)

Type I	Bilateral hilar and/or mediastinal adenopathy (80%)
Type II	Bilateral hilar and/or adenopathy with parenchymal infiltrates (68%)
Type III	Parenchymal infiltrates alone (33%)
Type IV	Fibrosis (irreversible)

flammatory response with an increase in lymphocyte count, total protein and angiotensin-converting enzyme (ACE) levels.

2.6 Cardiac Manifestations

Cardiac clinical manifestations of sarcoidosis are a rare, potentially life-threatening condition which is clearly under-diagnosed. Indeed, one-half of deaths from sarcoidosis were related to cardiac sarcoidosis.[7] Any area (pericardium, myocardium or endocardium) may be affected, but most lesions involve the myocardium and are responsible for heart blocks and failure. Using thallium-201 scans, one can detect a high proportion of nonperfusing myocardium which may not be clinically relevant. Even when asymptomatic, cardiac involvement is an indisputable indication for corticosteroid therapy.

2.7 Other Clinical Manifestations

Other exceptional clinical manifestations of this disease have been reported, such as interstitial nephropathy with renal insufficiency, ear, nose and laryngopharynx involvement, and cirrhosis.

3. Laboratory and Scintigraphic Explorations

Laboratory investigations of sarcoidosis are not specific but may contribute indirectly to support the diagnosis and participate in therapeutic monitoring. Serum analysis may indicate lymphopenia with a reduced CD4+/CD8+ ratio, hypergammaglobulinaemia, circulating immune complexes (in two-thirds of cases) and elevation of lymphocyte activation markers [β_2-microglobulin and interleukin-2 receptor (soluble CD25)]. Hypercalcaemia with hypercalciuria can be observed in about 25% of cases, reflecting an increase in 1,25-dihydroxyvitamin D_3 synthesis (probably by alveolar macrophages and sarcoid granulomas) and in intestinal calcium absorption. Elevated serum levels of ACE occur in approximately 60% of patients. This test appears to reflect the total body granulomatous burden and may be used to measure indirectly the response to treatment[1].

Due to its binding properties to the surface of mononuclear cells infiltrating inflammatory sites, gallium-67 has been proposed as a useful tool for the exploration of active sarcoidosis. However, the increased uptake seen on scans performed on the lung, the mediastinum, the parotid gland or the eye is aspecific and sometimes inconsistent. Therefore, gallium-67 scintigraphy may be more useful to assess the localisation and extent of sarcoidosis than for therapeutic monitoring.

Bronchoalveolar lavage fluid (BAL) analysis shows an increase in number and activity of T helper cells.[1] These cytological anomalies are not specific for sarcoidosis and are not currently considered to be clinically useful for therapeutic decisions or to predict functional deterioration. Nevertheless, BAL analysis remains helpful to exclude granulomatous infection.

Tuberculin skin tests are also very useful in the evaluation of suspected sarcoidosis by excluding tuberculosis from the primary diagnosis. However, because of the cutaneous anergy observed with sarcoidosis, other appropriate determinations should also be performed.

In view of the increased risk in HIV-infected patients for lymphoma and granulomatous infection, 2 common differential diagnoses of endothoracic sarcoidosis (table III), HIV serological tests should be performed and risk factors for HIV excluded through patient interview.

The Kveim antigen test (production of a nodule containing noncaseating granulomas by intradermal injection of 0.2ml of a 10% saline suspension of sarcoid tissue) is no longer in widespread use.

Table III. Differential diagnosis of pulmonary manifestations of sarcoidosis

Infectious diseases (tuberculosis, mycosis, others)[a]
Lymphoma,[a] Hodgkin's disease
Berylliosis and other occupational lung disorders
Carcinomatous lymphangitis
Hypersensitivity pneumonitis
Miliary form of histiocytosis X

a Increased risk in HIV disease.

Nevertheless, the test is still employed in some centres with adequate experience and remains a very specific and fairly sensitive investigation.

4. Histological Characteristics and Exploration

Epitheloid noncaseating granulomas are the hallmark histological findings of sarcoidosis. They are composed of epitheloid cells, macrophages and multinucleated giant cells surrounded by T helper lymphocytes and fibroblasts in the absence of caseating necrosis.[8] This microscopic pattern remains nonspecific, and one must exclude infectious or other identifiable agents responsible for such histological lesions, especially for the pulmonary manifestations shown in table III. Sarcoid granulomas may resolve and are frequently replaced with fibrous elements. Granulomatous lesions can be found in almost any tissue of the body, even in organs without any clinical signs, but are most frequently found in the lung, lymph nodes, liver, spleen and muscles. All these localisations may constitute a site for histological sampling.

The choice of sample will depend on radiographic and clinical manifestations and technical ease of the biopsy. The least aggressive sites of biopsy are cutaneous lesions, palpable peripheral lymph nodes, bronchi, sublingual salivary glands and muscles. Transbronchial lung biopsy may be a more profitable sample (46% with 1 sample to 90% with 4 samples[9]), but it is sometimes (in about 5% of procedures) complicated by pneumothorax and haemoptysis.

Mediastinal samples by mediastinoscopy and surgical pulmonary biopsy are rarely necessary, but may ensure a satisfactory diagnosis in atypical pulmonary forms (unilateral, nodular).

5. Treatment

Although sarcoidosis has been clinically and pathologically well described, its optimal treatment remains poorly defined.[8,10] Major treatment modalities are outlined in table IV.

Table IV. Proposed treatment for sarcoidosis

Conventional
Systemic or local corticosteroids
Alternative
Chloroquine or hydroxychloroquine
Methotrexate
Experimental (or case reports only)
Chlorambucil
Azathioprine
Cyclosporin
Cyclophosphamide
Thalidomide
Others
Symptomatic conventional treatment
Organ transplantation

5.1 Observation

The clinical evolution of the majority of patients with sarcoidosis is spontaneously favourable without any organ dysfunction. Thus, they require no treatment but only regular monitoring. Such monitoring should include clinical and ophthalmological examination, chest radiograph, pulmonary function tests, electrocardiogram, blood cell count, hepatic enzymology and serum creatinine, calcium and ACE levels.

5.2 Systemic Corticosteroids

The indication, dosage and duration of corticotherapy in sarcoidosis are still matters of debate. Use of corticosteroids should be limited to patients presenting objective evidence of recent deterioration of pulmonary function, severe extrapulmonary disease, cardiac and neurological involvement, loss of vision or severe polyarthritis and polymyositis, with organ dysfunction or metabolic disorders (hypercalcaemia).[10] Although several studies have observed the efficacy of systemic corticosteroid therapy in short term response to disease symptoms,[11] controversy remains concerning the use of corticosteroids to modify the natural outcome of sarcoidosis.[10,12] About 45 to 50% of patients who present with stage III sarcoidosis

will experience progressive disease despite corticosteroid treatment. Moreover, corticosteroid therapy seems ineffective on fibrous lesions.[10]

Initial therapy should consist of oral prednisolone 0.5 to 1 mg/kg/day or its equivalent for 3 months, followed by a progressive tapering of the dosage to about 15 mg/day. In order to reduce adverse effects, alternate-day therapy can be used during the maintenance phase. The duration of the maintenance phase may vary according to the clinical situation and the therapeutic response, but is generally between 6 and 18 months. A lack of response to corticosteroid therapy is sometimes observed, and first requires a reconsideration of the diagnosis in order to exclude a corticosteroid-induced concomitant infectious disease. In case of contraindications to corticosteroid therapy or of a corticosteroid-resistant active disease with functional deterioration, alternative drugs have been proposed.

5.3 Antimalarials

The antimalarial agents chloroquine and hydroxychloroquine have been used successfully in sarcoidosis, most often to treat severe skin sarcoid lesions and occasionally pulmonary manifestations or hypercalcaemia associated with sarcoidosis. Hydroxychloroquine 2 to 3 mg/kg/day induces a noticeable benefit after 1 month with a maximal improvement by 3 months, and allows other therapies such as corticosteroids to be discontinued.[13] It causes no severe toxicity, although an annual ophthalmological examination is required because of the potential adverse effects of antimalarials on the eye.

5.4 Methotrexate

The use of high dosage (25 to 75 mg/week) methotrexate in sarcoidosis was proposed 20 years ago.[14] However, recent experience in rheumatoid arthritis has led to its reapplication at lower dosages in sarcoidosis.[15] Low dosage (5 to 15 mg/week) methotrexate appears to be an effective, well-tolerated and corticosteroid-sparing alternative therapy for refractory pulmonary,[15] extrathoracic, cutaneous and ocular,[16] neurological[17] and hepatic[15,19] forms of sarcoidosis. A long term benefit (at least 2 years) with a significant corticosteroid-sparing effect has recently been reported for lung,[17] skin,[18] central nervous system[18] and musculoskeletal[19] complications of sarcoidosis. Prolonged methotrexate treatment may be associated with some hepatotoxicity, and most clinicians monitor liver function tests. Nevertheless, the value of regular liver function tests is poor and liver biopsies are proposed for identifying patients with subclinical hepatotoxicity.[18]

5.5 Other Immunosuppressive Agents

Published reports on the use of immunosuppressive agents such as azathioprine, cyclosporin, cyclophosphamide and thalidomide are scarce, with little information on the long term efficacy of these drugs. Chlorambucil was the most commonly used immunosuppressive agent; it has an effective corticosteroid-sparing effect in recalcitrant forms of sarcoidosis.[20] Its use remains limited because of a significant association with superinfection and the possibility of malignancies occurring after its continuous use.[15]

5.6 Topical Corticosteroids

High dosage inhaled corticosteroids (e.g. budesonide) have no substantial effects on pulmonary sarcoidosis. Local corticosteroid therapy may be effective for ocular and cutaneous sarcoid localisations. Potassium para-aminobenzoate may soften keloids and fibrotic lesions.

5.7 Symptomatic Treatment

Symptomatic treatment is also necessary in some clinical conditions arising from sarcoidosis. Such treatment includes antiarrythmic therapy, pacemaker implantation, heart failure medication, oxygen therapy, aerosol therapy, and exceptionally tracheostomy or anticonvulsant therapy.

5.8 Organ Transplantation

Lung and/or heart transplantation has occasionally been performed, but is accompanied by concerns about recurrent disease in the graft.

6. Conclusion

Recognition of sarcoidosis, a systemic disorder of unknown aetiology, includes compatible radiological and clinical presentation with histological evidence of noninfectious and noncaseating epitheloid cell granulomas.

The decision to treat and the optimal therapy remain poorly defined. In severe cases, corticosteroid therapy always constitutes the first approach. Antimalarial drugs or, more recently, low dosage methotrexate have shown prolonged benefit in refractory or corticosteroid-dependent forms of sarcoidosis. The long term administration of immunosuppressive drugs is uncommon and is not supported by adequate evidence.

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