CHAPTER 17

Diagnostic approach to sarcoidosis

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There is no single diagnostic test for sarcoidosis. The presence of noncaseating granulomas in a single organ, such as skin, does not establish a diagnosis of sarcoidosis. The finding of a granuloma is not specific for this disease, since many other conditions can cause granulomas.

The diagnosis of sarcoidosis is based on the following criteria: 1) a compatible clinical and/or radiological picture; 2) histological evidence of noncaseating granulomas; and 3) exclusion of other diseases capable of producing a similar histological or clinical picture.

In suspected sarcoidosis, the diagnostic procedures aim to accomplish the following goals [1]: 1) provide histological confirmation of the disease; 2) evaluate the extent and severity of organ involvement; 3) assess whether the disease is stable or likely to progress; and 4) determine if the patient will benefit from treatment.

Initial presentation

As sarcoidosis is a multi-organ disorder, patients may present initially to various organ specialists, depending on the symptoms. They may be seen by an ophthalmologist, a dermatologist, a rheumatologist, or any other specialist who will then perform the appropriate organ-specific examinations. If sarcoidosis is suspected or confirmed, the patient should be referred to a pulmonary specialist who would then take over the management of the patient, since the intrathoracic manifestations are the most frequent, and the pulmonary specialist usually sees most of the patients. If there is a need for consultation of another organ specialist during the follow-up, the pulmonary physician will transfer the patient, but should keep the general management of the patient during the course of his disease. In this regard, the management of patients with sarcoidosis requires a multidisciplinary approach.

Compatible clinical picture

Nonspecific constitutional symptoms, including fever (generally low-grade, but up to 40°C has been observed), weight loss (usually limited to 2–6 kg during the 10–12 weeks prior to presentation), and malaise are present in about one-third of patients, whereas fatigue and weakness can be seen in up to 70% of patients [2]. Sarcoidosis should always be included in the differential diagnosis of fever of unknown origin.

The clinical findings related to the involvement of specific organs vary in frequency.

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Dyspnoea and cough are often reported, since pulmonary involvement is the most frequent.

There are two different types of onset in sarcoidosis patients. Acute sarcoidosis has an abrupt onset and may present as Löfgren's syndrome, which is characterised by bilateral hilar adenopathy, ankle arthritis, erythema nodosum and frequently constitutional symptoms. Generally, chronic sarcoidosis has an insidious onset, and organ-related symptoms are often related to the pulmonary infiltration. Constitutional symptoms are less common than in the acute form.

Compatible radiographic picture

The chest radiographic findings vary to a great extent and they are discussed in detail in chapters 8 and 18 of this Monograph. Clinical and radiological findings alone are highly reliable in patients with stage I disease (accuracy 98%); the diagnostic reliability in stage II disease is also good (89%), but it is less for stage III (52%) or stage 0 (23%) disease [3, 4]. In a classical study of 100 consecutive patients with bilateral hilar adenopathy (BHL), over 95% of asymptomatic individuals with BHL and normal physical examination had sarcoidosis [5]. Malignancies were the cause of BHL in 11 out of 100 patients, and all were symptomatic. Therefore, histological confirmation may not be needed in asymptomatic patients who have symmetrical BHL. However, when the hilar lymph adenopathy is asymmetrical, massive or associated with large paratracheal enlargement, biopsy confirmation is strongly advised. In patients with a classical Löfgren's syndrome, biopsies are usually not necessary. Biopsy of erythema nodosum should be avoided, since histopathology shows no granuloma but nonspecific inflammation and vasculitis.

It is important to ask for previous chest radiographs. If they can be provided and show minor BHL, which may have been overlooked, and later show the development to stage II disease, such characteristic changes during the course may be sufficient to allow a diagnosis of sarcoidosis without biopsy confirmation.

Biopsy procedures and BAL

Biopsies can be obtained from easily accessable organs, such as peripheral lymph nodes, the skin, or the nasal mucosa. Historically, biopsies of scalene lymph nodes or mediastinoscopy were often performed. Nowadays, fiberoptic bronchoscopy with mucosal biopsy, transbronchial lung biopsy, transbronchial needle aspiration, and bronchoalveolar lavage (BAL) is the recommended procedure of choice [1]. The risks of the procedures are very low in experienced hands. The diagnostic yield of transbronchial lung biopsy is high, reaching up to 80%, if four to five adequate samples are obtained [6]. Bronchial mucosal biopsies should also be taken since the histological demonstration of granuloma is possible in 40–60%, even when the bronchial mucosa is grossly normal. When gross endoscopic findings, such as mucosal nodularity, oedema or hypervascularity are present, the yield may reach 90% [7].

The BAL fluid shows an increase in lymphocytes in 90% of sarcoidosis patients at the time of diagnosis. Such a BAL lymphocytosis is nonspecific and seen in many other disorders. When interpreting the cell differentials in regard to the differentiation of sarcoidosis *versus* other disorders, not a single parameter is important, but a combination of several features including: a normal or only mildly elevated total cell count with a predominance of lymphocytes, usually a normal percentage of eosinophils and neutrophils, and a lack of plasma cells and foamy alveolar macrophages is characteristic

for sarcoidosis. Recently, DRENT *et al*. [8] were able to differentiate between major interstitial lung disorders with a computer program for BAL data, using a discriminate analysis of logistic regression, with excellent accuracy [8]. A BAL CD4+/CD8+ ratio of >3.5 is very specific for sarcoidosis. Three independent groups have shown very similar values for the sensitivity and specificity of BAL CD4+/CD8+ ratios [9–11]. A ratio of >3.5 has a sensitivity of 52–59% and a specificity of 94–96%. The three studies reached similar conclusions; in patients with a clinical/radiological picture typical of sarcoidosis, an elevated CD4+/CD8+ ratio in BAL may confirm the diagnosis and obviate the need for confirmation by additional biopsy. In the study of WINTERBAUER *et al.* [10], transbronchial lung biopsy had a specificity of 89% for the distinction between sarcoidosis and other forms of diffuse lung disease, and was, therefore, no better than the CD4+/CD8+ ratio for this distinction. A recent study aimed to quantify how the likelihood for a given diagnosis changes with the knowledge of BAL cell differentials and the CD4+/CD8+ ratio. WELKER *et al.* [12] found that, when lymphocytes were combined with the CD4+/CD8+ ratio, the probability of sarcoidosis was doubled if the CD4+/CD8+ ratio was high. They were able to demonstrate an added informative value of the CD4+/CD8+ ratio, especially in sarcoidosis and extrinsic allergic alveolitis [12].

If bronchoscopic biopsies or BAL failed and no other easily accessible sites are identified, mediastinoscopy or surgical lung biopsy (usually by VATS) may be indicated. Biopsy of the liver is not specific and not recommended as a routine procedure. A detailed comparison of the biopsy procedures and the histopathological changes is provided in chapter 6 of this Monograph.

Additional investigations

Several tests are recommended in the initial evaluation of sarcoidosis as routine procedure for all patients (table 1). Pulmonary function tests have only a modest correlation with the chest radiograph. They provide a baseline for detection of improvement or deterioration during the further course of the disease, and should be done at the time of diagnosis even in patients without pulmonary signs and symptoms. Only 20% of patients with stage I disease show abnormalities in pulmonary function tests, compared with 40–70% in the other radiographic stages [13]. The most sensitive tests are the carbon monoxide diffusion capacity of the lung and the vital capacity. The typical finding is a restrictive pattern, whereas an obstructive pattern is seen in up to 30% of patients, and bronchial hyperreactivity is present in 25%. Changes in gas exchange with exercise are even more sensitive than lung function tests at rest [14]. Blood testing is performed to exclude hypercalcaemia and significant hepatic, renal or haematological

Table 1. – Recommended tests for initial evaluation of sarcoidosis

Type of evaluation
History (occupational and environmental exposure, symptoms)
Physical examination
Posteroanterior chest radiography
Pulmonary function tests: spirometry and carbon monoxide diffusion capacity
Peripheral blood counts: white blood cells, red blood cells, platelets
Serum chemistries: calcium, liver enzymes, creatinine, blood urea nitrogen
Urine analysis
Electrocardiography
Routine ophthalmologic examination
Tuberculin skin test

Adapted from [1].

involvement. Routine ophthalmological investigation, including an initial slit lamp examination, is obligatory in all patients in order to exclude a clinically silent uveitis.

Chest computed tomography (CT) scans are not routinely needed. In some patients (~30% of patients, according to the experience of the present authors) high-resolution CT (HRCT) is indicated for the following reasons. 1) Atypical clinical and/or chest radiographic findings; 2) a normal chest radiograph but a clinical suspicion of the disease; 3) suspected complications of lung disease, such as bronchiectasis, aspergilloma, and traction emphysema; or 4) superimposed infection or malignancy. The characteristic findings of HRCT are described in detail in chapter 18. Briefly, apart from hilar and mediastinal adenopathy, the characteristic findings are nodular infiltrates with bronchovascular and subpleural distribution, thickened interlobular septa, architectural distortion, and conglomerate masses originating from coalescence of nodules in the perihilar, peribronchovascular, or subpleural regions [15]. In contrast to the conventional chest radiographic findings, the appearance and the extent of disease on HRCT, such as thickening or irregularity of the bronchovascular bundle, intraparenchymal nodules, septal and nonseptal lines and focal pleural thickening, correlate with parameters of respiratory functional impairment, both at rest and at maximal exercise [16].

Further investigations are needed if extrapulmonary sarcoidosis is suspected. These investigations are discussed in detail in the organ manifestation chapters of this monograph. It is important to recognise extrathoracic involvement early, since the prognosis is dictated not only by the radiographic stages, but also by certain organ manifestations, many of those having an adverse impact on prognosis (table 2) [17].

Assessment of activity

The term "activity" is frequently used in sarcoidosis, but often misinterpreted. Activity should not be mixed up with the extent or severity of the disease (*i.e.* the number of involved organs, or the density of granulomas within an involved organ), should also not be associated with unfavourable prognosis (*e.g.* the highly active acute disease, manifesting as Löfgren's syndrome, has the best prognosis), and also not be misinterpreted with the necessity of initiating corticosteroid therapy [18]. Active disease means that the disease has not yet come to a rest, that there is still ongoing T-cell and macrophage inflammation and granuloma formation (reflected by increased soluble interleukin (IL)-2 receptor levels or angiotensin-converting enzyme (ACE) levels) with the potential that the disease may progress, whereas inactive disease means that the disease has come to a rest and will probably not progress any further.

A long list of laboratory and cell biological markers has been discussed as potential indices of active disease, either in serum or in BAL fluid [17–19]. However, none of them

Table 2. – Adverse prognostic factors in sarcoidosis

Type of factor
Lupus pernio
Chronic uveitis
Age of onset >40 yrs
Chronic hypercalcaemia
Nephrocalcinosis
Black race
Progressive pulmonary sarcoidosis
Nasal mucosal involvement
Cystic bone lesions
Neurosarcoidosis
Myocardial involvement

can be recommended for routine assessment, perhaps with the exception of serum ACE, reflecting the granuloma burden, and the soluble IL-2 receptor, reflecting the activity of the T-cell component [20–22]. Serum ACE may be useful in monitoring the course of disease. Increased ACE activity will usually be reduced within a few weeks of the start of corticosteroid treatment. In the future, revised normal ranges, corrected for the ACE genotype, might improve the clinical significance of this marker [23]. The quantification and subtyping of lymphocytes in BAL fluid have not fulfilled the early promise of being useful markers of disease activity. The prognostic value of increased neutrophils seems to be more promising. Two independent studies found a higher number of neutrophils in BAL fluid in a group of patients who deteriorated in the follow-up, but further experience and prospective studies are necessary to confirm this for the individual patient [20, 24].

At present, the best way to assess the activity of sarcoidosis is still through traditional clinical investigations. The clinical activity is assessed on the basis of onset, worsening or persistence of symptoms, or signs directly related to sarcoidosis. These may be constitutional symptoms, or the new development or changes of skin lesions, in combination with changes in chest radiography and lung function tests. However, it is of more clinical relevance to depict disease extent and severity than the activity of sarcoidosis in an individual patient.

Summary

The diagnostic approach to sarcoidosis is a complex procedure. There is no single diagnostic test for this disease. The diagnosis is based on three criteria: a compatible clinical and/or radiological picture, histological evidence of noncaseating granulomas, and exclusion of other diseases that may produce a similar histological or clinical picture. The diagnostic procedures should accomplish the following goals: 1) provide histological confirmation of the disease; 2) evaluate the extent and severity of organ involvement; 3) assess whether the disease is stable or likely to progress; and 4) determine if the patient will benefit from treatment.

The clinical picture depends on the type of onset. Acute sarcoidosis has an abrupt onset and may present as Löfgren's syndrome. Chronic sarcoidosis has an insidious onset, and organ-related symptoms are often caused by the pulmonary infiltration. It is important to know that nonspecific constitutional symptoms, including fever, weightloss, and fatigue, may occur in a high proportion of patients.

The chest radiographic findings have various diagnostic reliability: stage I disease has an accuracy of 98% and, thus, a high diagnostic reliability, stage II is still good (89%), but the diagnostic reliability is low in the other stages. Biopsies can be obtained from easily accessable organs, such as peripheral lymph nodes, or the skin. In most cases, fibreoptic bronchoscopy with various biopsy techniques is the recommended procedure of choice. In the bronchoalveolar lavage fluid, a lymphocytosis is quite sensitive, but less specific, whereas an increased CD4+/CD8+ ratio increase is less sensitive, but highly specific for sarcoidosis. Additional tests include pulmonary function testing, laboratory tests and screening for important extrathoracic organ involvement.

The best way to assess the activity remains through traditional clinical investigations, on the basis of onset, worsening or persistance of symptoms or signs directly related to sarcoidosis. No single biochemical or cell biological marker has a better predictive value for prognosis or disease state than the classic chest radiographic staging system.

Keywords: Activity, diagnostic approach, sarcoidosis, severity.

References

1. Hunninghake GW, Costabel U, Ando M, *et al.* American Thoracic Society/European Respiratory Society/World Association of Sarcoidosis and Other Granulomatous Disorders: statement on Sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis* 1999; 16: 149–173.
2. Drent M, Wirnsberger RM, De Vries J. Association of fatigue with an acute phase response in sarcoidosis. *Eur Respir J* 1999; 13: 718–722.
3. Hiraga Y, Hosoda Y. Acceptability of epidemiological diagnostic criteria for sarcoidosis without histological confirmation. *In*: Mikami R, Hosoda Y, eds. Sarcoidosis. Tokyo, University of Tokyo Press, 1981; pp. 373–377.
4. Reich JM, Bouns MC, O'Connor EA, Edwards MJ. Mediastinoscopy in patients with presumptive stage I sarcoidosis. *Chest* 1998; 113: 147–153.
5. Winterbauer RH, Belic N, Moores KD. A clinical interpretation of bilateral hilar addenopathy. *Ann Intern Med* 1973; 79: 65–71.
6. Gilman MJ, Wang KP. Transbronchial lung biopsy in sarcoidosis: an approach to determine the optimal number of biopsies. *Am Rev Respir Dis* 1980; 122: 721–724.
7. Armstrong JR, Radke JR, Kvale PA, *et al.* Endoscopic findings in sarcoidosis. *Ann Otol* 1981; 90: 339–434.
8. Drent M, Jacobs JA, Cobben NA, *et al.* Computer program supporting the diagnostic accuracy of cellular BALF analysis: a new release. *Respir Med* 2001; 95: 781–786.
9. Costabel U, Zaiss AW, Guzman J. Sensitivity and specifity of BAL findings in sarcoidosis. *Sarcoidosis* 1992; 9: Suppl. 1, 211–214.
10. Winterbauer RH, Lammert J, Selland M, *et al.* Bronchoalveolar lavage cell populations in the diagnosis of sarcoidosis. *Chest* 1993; 104: 352–361.
11. Thomeer M, Demedts M. Predicitive value of CD4/CD8 ratio in bronchoalveolar lavage in the diagnosis of sarcoidosis (abstract). *Sarcoidosis Vasc Diffuse Lung Dis* 1997; 14: Suppl. 1, 36.
12. Welker L, Jörres RA, Costabel U, Magnussen H. Predictive value of BAL cell differentials in the diagnosis of interstitial lung diseases. *Eur Respir J* 2004; 24: 1000–1006.
13. Lynch JP 3rd, Kazerooni EA, Gay SE. Pulmonary sarcoidosis. *Clin Chest Med* 1997; 18: 755–785.
14. Delobbe A, Perrault H, Maitre J, Robin S, *et al.* Impaired exercise response in sarcoid patients with normal pulmonary function. *Sarcoidosis Vasc Diffuse Lung Dis* 2002; 19: 148–153.
15. Wells A. High resolution computed tomography in sarcoidosis: a clinical perspective. *Sarcoidosis Vasc Diffuse Lung Dis* 1998; 15: 140–146.
16. Drent M, De Vries J, Lenters M, *et al.* Sarcoidosis: assessment of disease severity using HRCT. *Eur Radiol* 2003; 13: 2462–2471.
17. Costabel U. Sarcoidosis: clinical update. *Eur Respir J* 2001; 18: Suppl. 32, 56s–68s.
18. Costabel U, du Bois RD, Eklund A. Consensus conference: activity of sarcoidosis. *Sarcoidosis* 1994; 11: 27–33.
19. Costabel U, Teschler H. Biochemical changes in sarcoidosis. *Clin Chest Med* 1997; 18: 827–842.
20. Ziegenhagen MW, Rothe ME, Schlaak M, Müller-Quernheim J. Bronchoalveolar and serological parameters reflecting the severity of sarcoidosis. *Eur Respir J* 2003; 21: 407–413.
21. Grutters JC, Fellrath JM, Mulder L, *et al.* Serum soluble interleukin-2 receptor measurement in patient with saroidosis: a clinical evaluation. *Chest* 2003; 124: 186–195.
22. Rothkrantz-Kos S, van Dieijen-Visser MP, Mulder PGH, Drent M. Potential usefulness of inflammatory markers to monitor respiratory functional impairment in sarcoidosis. *Clin Chem* 2003; 49: 1510–1517.
23. Sharma P, Smith I, Maguire G, *et al.* Clinical value of ACE genotyping in diagnosis of sarcoidosis. *Lancet* 1997; 349: 1602–1603.
24. Drent M, Jacobs JA, De Vries J, *et al.* Does the cellular bronchoalveolar lavage fluid profile reflect the severity of sarcoidosis? *Eur Respir J* 1999; 13: 1338–1344.