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REVIEW

Sarcoidosis: clinical update

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ABSTRACT: Many advances have been made regarding sarcoidosis in the past 2 decades. As a result, sarcoidosis is now defined as a multisystem disorder with a heightened cellular immune response at sites of disease activity in patients with a predisposition for sarcoidosis and a presumed exposure to as yet unknown transmissible environmental agents.

Recent International Consensus Statement recommendations regarding diagnosis and therapy have been published. The diagnosis of sarcoidosis is based on a compatible clinical and/or radiological picture, histological evidence of noncaseating granulomas and exclusion of other diseases capable of producing a similar histological or clinical picture.

Therapy is based on corticosteroids, although there are indications of valuable alternatives. Except for life- and sight-threatening organ involvement, it should be carefully considered whether the patient might benefit from treatment. For asymptomatic pulmonary sarcoidosis, a watch and wait approach is appropriate; treatment should mainly be considered if symptoms develop or lung function deteriorates.
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Sarcoidosis has been characterized for over a century, initially through its skin manifestations, and later, with the use of routine and screening chest radiography, as a frequently asymptomatic disease with hilar lymphadenopathy and pulmonary infiltration. The disease is an immunological disorder par excellence, involving many components of the immune system. With the introduction of bronchoalveolar lavage (BAL) as a major research tool ~20 yrs ago, the characteristic features of a heightened cellular immune response at sites of disease activity have been identified. Previously, sarcoidosis had been misinterpreted as an immune deficiency disease with depressed cellular immunity because of the cutaneous anergy.

The descriptive definition of sarcoidosis, as reported at the World Congress in Kyoto in 1991 [1], reads as follows: "Sarcoidosis is a multisystem disorder of unknown cause. It commonly affects young and middle-aged adults and frequently presents with bilateral hilar lymphadenopathy, pulmonary infiltration, ocular and skin lesions. Other organs may also be involved. The diagnosis is established when clinicoradiological findings are supported by histological evidence of noncaseating epithelioid cell granulomas. Granulomas of known causes and local sarcoid reactions must be excluded. Frequently observed immunological features are depression of cutaneous delayed-type hypersensitivity and increased CD4/CD8 ratio at the site of involvement. Circulating immune complexes along with the signs of B-cell hyperactivity may also be detectable. The course and prognosis may correlate with the mode of the onset and the extent of the disease. An acute onset with erythema nodosum or asymptomatic bilateral hilar lymphadenopathy usually heralds a self-limiting course, whereas an insidious onset, especially with multiple extra-pulmonary lesions, may be followed by relentless progressive fibrosis of the lungs and other organs."

It is evident that many immunological features are part of this definition. After briefly discussing the current understanding of epidemiology, aetiology and immunology, this review mainly focuses on the present diagnostic approach to and management of the disease, taking into account new advances related to sarcoidosis. Importantly, for the first time in the history of sarcoidosis, a Consensus Statement by the American Thoracic Society (ATS), the European Respiratory Society (ERS), and the World Association of Sarcoidosis and other Granulomatous Disorders (WASOG) has recently been published to update clinicians and scientists on the disease, and to help in the management and care of patients, by giving recommendations regarding diagnosis and therapy [2].

Epidemiology

Significant heterogeneity in prevalence, disease presentation and severity of sarcoidosis occurs among different ethnic and racial groups and in various countries. The prevalence ranges from less than one case to 40 cases per 100,000. The highest prevalence rates, with >50 cases per 100,000, have been reported in Scandinavian countries and the US African-American population [3]. Sarcoidosis is common in Central

Europe, USA and Japan. It appears less frequently in Central and South America, other Asian countries and Africa. Sarcoidosis in African-Americans is more severe, while Caucasians are more likely to present with asymptomatic disease. Overall mortality is 1–5% [2]. In Japan, the most frequent cause of death in sarcoid patients is from myocardial involvement, whereas respiratory failure is more common elsewhere.

Erythema nodosum associated with acute disease and good prognosis is the presenting symptom in 18% of Finnish and 30% of British sarcoidosis patients, whereas it is very rare in African-Americans and the Japanese [3, 4]. In contrast, lupus pernio and other cutaneous manifestations are associated with a chronic course and appear more frequently in African-Americans than in Caucasians [3]. Spatial and familial clustering of sarcoidosis may occur. This may indicate shared exposure to an environmental agent or a genetic predisposition for the disease expression.

Sarcoidosis shows a predilection for adults <40 yrs, peaking between 20–29 yrs. There is a slight female predominance. In Scandinavian countries, Germany and Japan, there is a second peak incidence in females >50 yrs of age [2]. Sarcoidosis rarely occurs in children and the elderly.

Aetiology

The aetiology is still unknown, although there has been an intensive search for possible aetiological agents. The general concept has emerged that sarcoidosis results from the exposure of genetically susceptible individuals to specific environmental agents. There are several lines of evidence supporting this concept, which are outlined in more detail in the Report of Working Group 2 by VERLEDEN *et al.* [5] in this Supplement.

Sarcoid constitution

There is familial clustering of sarcoidosis [6]. In Ireland, 2.4% of sarcoidosis cases occur among siblings [7]. The most common relationship is between brother and sister, followed by mother and offspring.

A genetic predisposition may explain the heterogeneity in disease presentation and severity among different ethnic and racial groups. The human leukocyte antigen (HLA)-type A1/B8/Cw7/DR3 carries a good prognosis and correlates with acute disease, including Löfgren′s syndrome, whereas chronic disease is associated with B13 in Japanese subjects and BW15 in African-Americans. In a Scandinavian study, DR17 was associated with a better pulmonary function, a good prognosis and short disease duration. In contrast, DR14 and DR15 were related to a more prolonged disease course [8–11]. The HLA-B22 phenotype is associated with disseminated systemic disease in Italians [9].

Gene polymorphisms of proinflammatory cytokines may also be associated with the expression of the disease. One such bi-allelic polymorphism is found in the tumour necrosis factor (TNF)-α gene at position 308 in the promoter region. One of its alleles, the TNFA2 allele, is linked to elevated TNF-α levels. However, a recent study showed no association between the expression of this allele and an exaggerated release of TNF-α in sarcoidosis patients, casting some doubt on its pathogenetic relevance [12]. Also, the TNF-α genotype is not associated with susceptibility to sarcoidosis. A shift to the TNFA2 allele was observed only in the subgroup of patients with Löfgren′s syndrome, not the entire sarcoidosis cohort [13].

Another polymorphism of potential relevance is found in the angiotensin converting enzyme (ACE) gene [14, 15]. Although the polymorphism influences the serum ACE levels (the DD (deletion) genotype being associated with high, the ID (insertion/deletion) genotype with intermediate, and the II (insertion/insertion) genotype with the lowest levels), most studies failed to show an association between the ACE genotype and the risk of developing sarcoidosis [16–18]. Other studies showed such an association with the DD genotype only in African-Americans [19] or reported an increased frequency of the DD genotype only in sarcoidosis patients with autoimmune manifestations [20]. Furthermore, only one study has found the ACE DD genotype to be associated with a poorer prognosis than the other genotypes [21].

Vitamin D receptor gene polymorphisms have recently been investigated, and the B allele has been suggested to be a genetic risk factor for sarcoidosis [22]. For more detailed insights into the complex issues of genetic components in sarcoidosis, the reader is referred to an exhaustive review on this topic recently published in this journal [23] and to the Report of Working Group 2 by VERLEDEN *et al.* [5] in this Supplement.

Exposure to transmissible environmental agents

Immunological abnormalities in sarcoidosis are characterized by features of an antigen-triggered cell-mediated immune response. The pattern of cytokine production in the lungs is most consistent with a Th1-type immune response [11, 24–26].

Seasonal clustering of sarcoidosis in the early spring, spatial clustering in the Isle of Man, and work-related clustering in nurses and other healthcare workers are consistent with the concept of an infectious cause of the disease [2]. In addition, sarcoidosis can be transmitted *via* transplanted organs: recipients of cardiac or bone marrow transplants from sarcoidosis patients have subsequently developed sarcoidosis [27].

Several infectious organisms have been implicated as possible agents in the aetiology of sarcoidosis, *e.g.* viruses (human herpes virus, retrovirus, Epstein-Barr virus (EBV)), bacteria (*Propionibacterium acnes*, *Borrelia burgdorferi*, Mycoplasma, Chlamydia, Nocardia), and mycobacteria (*Mycobacteria tuberculosis*, *Mycobacteria paratuberculosis*, cell wall deficient mycobacteria) [2, 11, 28]. Serological studies have detected increased serum antibodies against several of

these agents, but this probably reflects an epiphenomenon due to increased polyclonal immunoglobulin production by the hyperactive B-cell system, rather than a specific response to a causative agent.

Unfortunately, even with the advent of molecular tools, there is no definite proof of a specific infectious aetiological agent in sarcoidosis: no infective or other agent has been consistently isolated or cultured.

Immunopathogenesis

Immunological abnormalities are characterized by the accumulation of activated CD4+ T-cells of the Th1-type and macrophages at sites of ongoing inflammation, notably in the lung [11, 25, 26, 29]. Cytokines and other mediators produced by these cells contribute to granuloma formation. Macrophages show enhanced expression of major histocompatibility complex (MHC)-class-II and other costimulatory accessory molecules. The elevated accessory function is mainly mediated by the expression of CD54 and CD80 [30, 31]. The enhanced antigen presenting capacity of macrophages is probably induced by interaction with the potential sarcoidosis antigen or antigens. These alveolar macrophages recognize, process and present the putative antigen to Th1 lymphocytes. The activated sarcoid macrophages produce interleukin (IL)-12, a key cytokine in inducing the shift towards a Th1 profile and stimulating interferon (IFN)-γ production by lung T-cells [32–36]. The activated T-cells in turn release IL-2 and chemotactic factors for blood monocytes, leading to further recruitment of monocytes/macrophages to the site of disease activity. IFN-γ is able to further activate macrophages, and IL-2 activates and expands the various T-lymphocyte clones [37–40]. IFN-γ is also important for the transformation of macrophages into giant cells (macrophage fusion factor), which are important building blocks of the granuloma [41]. The proinflammatory macrophage cytokines IL-1, IL-6 and TNF-α are essential to induce and maintain granuloma formation, and all are increased in sarcoidosis [42], whereas the anti-inflammatory cytokine IL-10 is not increased in sarcoidosis [32, 43]. However, controversial results regarding its messenger ribonucleic acid (mRNA) expression by BAL cells have been reported [32, 33]. The role of transforming growth factor (TGF)-β is also still controversial. One study found high TGF-β release from BAL cells in active disease undergoing spontaneous remission [43], whereas another group reported increased BAL levels in patients with altered lung function [44].

Activated macrophages are able to secrete various fibroblast growth factors. They probably contribute to fibroblast proliferation, collagen synthesis, and development of fibrosis in sarcoidosis, although this last step in the pathogenesis, the passage from granuloma to fibrosis, is not well understood. No studies have shown why lung disease persists in some patients but not in others. No studies have shown how persistent disease results in lung injury and fibrosis. A shift from a Th1 to a Th2 phenotype with secretion of IL-4 and IL-10 may be important for persistent disease, whereas the Th1 cytokines are likely to favour the granulomatous response [26]. Definitive longitudinal data on lung Th1 and Th2 response in patients with pulmonary sarcoidosis are lacking. Studies of the different phases (early alveolitis, granuloma, fibrosis) are needed to understand the regulatory immune mechanisms that govern the outcome of the disease.

Since the first report by MOLLER *et al.* [45] on a bias in the usage of certain T-cell antigen receptors (TCR) by T-cells in the lungs of sarcoidosis patients, numerous studies have confirmed the existence of T-cells that have a restricted TCR repertoire in involved tissues [46]. A preferential usage of TCR Vβ2 and/or Vβ8 has been reported. One study showed a strong association between the HLA-DR17 haplotype and the expression of TCR Vα2.3 by CD4+ lung T-cells [47]. There was also a relationship between Vα2.3+ CD4+ T-cells in BAL and clinical signs of disease activity [47]. A bias in the usage of certain TCR genes indicates oligoclonal proliferation of T-cells, which may be consistent with stimulation of T-cells by an antigen or a superantigen. Since T-cells in BAL from healthy individuals have not shown a preferential expression of particular TCR regions, the bias found in the lung in sarcoidosis would indicate that T-cells have been exposed to an antigen that is not normally present. It is still unclear, however, how helpful TCR studies will be in eliciting the aetiology of sarcoidosis.

Clinical presentation

Because sarcoidosis is a multiorgan disorder, patients may present to clinicians of different specialities. The clinical picture is very variable and depends on ethnicity, duration of illness, site and extent of organ involvement, and activity of the granulomatous process, which shows a tendency to wax and wane.

There are three different modes of clinical presentation: asymptomatic sarcoidosis; nonspecific constitutional symptoms; and symptoms related to specific organ involvement. The true numbers of asymptomatic patients cannot be reliably determined, since many of them escape diagnosis. These patients are usually detected by abnormal routine chest radiograph. In various series, 30–50% of patients were found to be asymptomatic at the time of diagnosis [48–49].

Constitutional symptoms are present in about one-third of patients, and more frequently in African-Americans. The symptoms include 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), fatigue and weakness, which can be disabling [50], and drenching night sweats [51]. Sarcoidosis should always be included in the differential diagnosis of fever of unknown origin.

The frequency of clinical findings related to the involvement of specific organs is variable, depending on how thoroughly the diagnostic investigations explore the extent of organ involvement (table 1).

There are two different types of onset in sarcoidosis

Table 1. – Organ involvement in sarcoidosis

Organ	% of patients
Mediastinal lymph nodes	95–98%
Lungs	>90%
Liver	50–80%
Spleen	40–80%
Eyes	20–50%
Peripheral lymph nodes	30%
Skin	25%
Nervous system	10%
Heart (clinically)	5%

patients. 1) Acute sarcoidosis has an abrupt onset, is more frequent in Caucasians than African-Americans, and may present as Löfgren's Syndrome, which is characterized by bilateral hilar adenopathy, ankle arthritis, erythema nodosum, and frequently constitutional symptoms including fever, myalgia, malaise and weight loss [52]. The prognosis is good and spontaneous remission usually occurs within 2 yrs. Rarely, erythema nodosum may relapse, even after many years. 2) Chronic sarcoidosis has an insidious onset. Organ-related symptoms, often related to pulmonary infiltration, such as cough and dyspnoea, predominate, whereas constitutional symptoms are much rarer than in the acute form. The course is often relapsing, with resolution being less likely and taking a more protracted time course than in the acute form.

Organ manifestations

Lungs

The lungs are affected in >90% of patients. Prominent symptoms are dyspnoea, dry cough, and chest pain, occurring in 30–50%. Haemoptysis is rare. In contrast to many other interstitial lung diseases, clubbing and fine crackles are not usually present [53]. There is a higher incidence of sarcoidosis in nonsmokers [54].

The chest radiograph types are shown in table 2. In type I disease, without radiological involvement of the lung parenchyma, biopsy can still reveal granulomata in the lung tissue in up to 80% of patients. A unilateral, and then mostly left-sided hilar lymph node enlargement, is extremely rare. Calcified hilar lymph nodes may occur in 5% of patients and are a sign of long-standing sarcoidosis, resembling the eggshell calcification described in silicosis. The most common type of lung infiltrate is diffuse with an interstitial reticulonodular pattern and upper lobe predominance. Areas of consolidation, even with associated air bronchograms, may also be present. Type IV disease represents the fibrotic stage, with shrinking of mainly the upper lobes, together with hilar retraction, deformity of the parenchymal structures with pleural adhesions to the diaphragm, bulla formation, cysts and honeycombing. Larynx, trachea and bronchi may also be involved, leading to stridor, airway obstruction and bronchiectasis. The incidence of bronchial hyperreactivity is increased. Pleural effusion, pneumothorax, severe pleural thickening are uncommon manifestations [55].

Table 2. – Chest radiographic stages of sarcoidosis

Stage		Frequency
0	Normal	5–10%
I	BHL	50%
II	BHL and parenchymal infiltrates	25%
III	Parenchymal infiltrates without BHL	15%
IV	Signs of fibrosis	5–10%

BHL: bilateral hilar lymphadenopathy.

Lymphoid system

Peripheral lymph nodes are enlarged in about one-third of patients and they may offer a good site for biopsy [56]. The spleen is frequently involved, in 40–80% of autopsy studies, but clinical symptoms due to splenomegaly (local pressure, haematological abnormalities due to hypersplenism) are rare [57]. A very unusual complication of massive splenomegaly is splenic rupture (spontaneous or traumatic).

Skin

Cutaneous involvement occurs in about one-quarter of the patients [58]. This is less frequent and usually less severe in Caucasians than in African-Americans. There are a number of skin manifestations ranging from small purplish papules to plaques and subcutaneous nodules. Small maculopapular eruptions may disappear during the course of the disease, whereas other lesions tend to wax and wane, including the unique variant of scar sarcoidosis. Lupus pernio is an indurated, bluish discoloration of the nose, cheeks, lips or ears, and usually heralds a poor prognosis. Erythema nodosum is a manifestation of acute sarcoidosis that is not associated with the presence of granulomas and usually subsides within 6–8 weeks. In this regard, biopsy of an erythema nodosum lesion is not useful, whereas other skin manifestations are good, noninvasive biopsy sites for granuloma demonstration.

Ocular involvement

Ocular lesions occur in 20–30% of patients and are most serious because of the threat of blindness [59]. Since eye involvement may be asymptomatic, every patient with sarcoidosis should undergo ophthalmological investigation, including slit lamp examination. The chronic form of uveitis may lead to glaucoma, cataract and blindness. Any part of the eye may be involved, but the most common lesion is uveitis. Acute anterior uveitis resolves spontaneously or after local therapy with corticosteroids, whereas posterior uveitis needs systemic treatment.

Heart

Clinical heart involvement occurs in 5% of patients, but the autopsy incidence may be much higher [60]. Sudden death may occur. The main manifestations are arrythmia of all types, conduction abnormalities, and congestive heart failure [61]. If a conventional electrocardiogram (ECG) shows any abnormality, 24-h Holter monitoring should be performed. Doppler-echocardiography may show cardiac dysfunction, especially diastolic dysfunction, in which case Thallium-201 (^{201}Tl)-scintigraphy is indicated. ^{201}Tl accumulates in normal myocardial cells. Segmental areas of decreased Tl uptake correspond to granulomata or fibrosis. In contrast to perfusion defects of cardiac ischaemia, the defects in sarcoidosis decrease in size during exercise. This phenomenon is called reversed distribution [62]. Coronary angiography is needed to exclude the possibility of coronary artery disease if myocardial sarcoidosis is suggested by ^{201}Tl-imaging. Endomyocardial biopsy has a low sensitivity of <50%. Thus, a sarcoidosis patient with ECG abnormalities and/or cardiac dysfunction and ^{201}Tl-imaging defects should be presumed to have cardiac involvement, even in the absence of a positive myocardial biopsy, and should be treated accordingly.

Nervous system

Neurological manifestations occur in <10% of patients [61, 63]. There is a predilection for the base of the brain. Some lesions tend to occur early and respond favourably to treatment. These include cranial nerve involvement, particularly facial palsies, and hypothalamic and pituitary lesions. In contrast, space-occupying masses, peripheral neuropathy and neuromuscular involvement occur later and are associated with a chronic course. One problem in making the diagnosis is the difficulty of obtaining histological proof. Frequently, the diagnosis of nervous system involvement rests on clinical features, together with demonstration of sarcoidosis in other organs and exclusion of other neurological diseases. Computed tomography (CT) and magnetic resonance imaging (MRI) are indicated in patients with neurological symptoms and signs. Gadolinium (Gd)-enhanced MRI may reveal involvement of brain parenchyma, meninges and spinal cord. MRI manifestations are, however, nonspecific. Cerebrospinal fluid reveals lymphocytosis, elevated protein and increased ACE. The triad of facial nerve palsy, parotitis and anterior uveitis is called Heerfordt syndrome and carries a good prognosis.

Liver involvement

This is usually clinically mild, with an asymptomatic increase in hepatic enzymes [64, 65]. The liver is palpable in only ~20% of patients. In contrast, granulomata on liver biopsy are found in up to 80% of patients. However, the liver should not be the site of first choice biopsy, since liver granulomas are formed in many other disorders. Occasionally, liver involvement is severe, leading to intrahepatic cholestasis, portal hypertension and hepatic failure, so that treatment is indicated.

Other organ involvement

Cystic bone lesions are rare and almost exclusively associated with chronic skin lesions. Joint pains occur in 25–39% of patients, but deforming arthritis is rare. Muscle involvement may cause proximal weakness. Corticosteroid-induced myopathy should be excluded. Renal involvement in sarcoidosis may result from hypercalcaemia/hypercalciuria, causing nephrocalcinosis, urolithiasis, and renal failure, and also from direct involvement of the kidneys by a granulomatous interstitial nephritis. Haematological abnormalities are rarely severe. Leukopenia occurs in as many as 40% of patients. The most likely mechanism is a redistribution of blood T-cells to the site of the disease. The most frequent endocrine manifestation is hypercalcaemia, occurring in 2–10%. Diabetes insipidus may occur as a result of pituitary or hypothalamic involvement [2, 66].

Diagnostic approach

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

In suspected sarcoidosis, the diagnostic procedures should attempt to accomplish the following four goals: 1) provide histological confirmation of the disease; 2) assess 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 therapy.

Biopsy procedures

The site for biopsy is dependent on the manifestation of the disease. Historically, biopsies of scalene lymph nodes or mediastinoscopy were often performed. Nowadays, transbronchial lung biopsy through a fibreoptic bronchoscope is the recommended procedure in most cases [2]. In experienced hands, the diagnostic yield is high, reaching 80–90% if $\geqslant$4–5 adequate samples are obtained [67]. Even in stage I disease, the yield may be 70–80% [68]. Bronchial mucosal biopsy should also be taken, since the histological demonstration of granuloma is possible in 40–60% of cases, even when the bronchial mucosa is grossly normal. When gross endoscopic findings such as mucosal nodularity, oedema or hypervascularity are present, the yield of endobronchial biopsies may exceed 90% [69]. These bronchoscopic biopsy procedures may be combined with BAL and studies of lymphocyte subpopulations. Three independent

groups have shown very similar values for the sensitivity and specificity of BAL CD4/CD8 ratios [70–72]. A ratio of >3.5 or 4.0 has a sensitivity of 52–59% and a specificity of 94–96%. These three studies reached a similar conclusion: in patients with a clinical picture typical of sarcoidosis, an elevated CD4/CD8 ratio in BAL may confirm the diagnosis and obviate the need for confirmation by additional biopsy [73]. It is important to note that in the study of WINTERBAUER *et al.* [71], transbronchial 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 in this regard.

Other possible sites for biopsy are visible skin lesions, the lips (minor salivary gland involvement), the conjunctiva, or superficial lymph nodes, if they are enlarged. Biopsy of erythema nodosum lesions is not useful as they do not show granulomas. In general, the easiest accessible biopsy site is the target for biopsy confirmation. Biopsy of the liver is nonspecific and not recommended. If bronchoscopic biopsies or BAL have failed and no other easily accessible sites are identified, mediastinoscopy or surgical lung biopsy may be indicated.

The basic histopathological lesion in sarcoidosis is the noncaseating epithelioid cell granuloma. This consists of radially arranged epithelioid cells, which are surrounded by a lymphocytic infiltration. Multinucleate giant cells of the Langhans′ type are present and may contain Schaumann and asteroid bodies. These granulomas may resolve spontaneously, leaving no scar, or may persist for a long time and may finally undergo hyalinization and fibrosis, which usually begins at the periphery and travels to the centre of the granuloma. This may lead to a loss of tissue architecture. In the lungs, the granulomas are located close to or within the connective tissue sheath of the bronchioles, subpleural and perilobular spaces, and small vessels (a lymphangitic distribution).

The patient without biopsy

Some patients refuse biopsies. In others, lung biopsy may be associated with an increased risk. 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 reliable for patients with stage III (52%) or stage 0 (23%) disease [74].

In this regard, a recent risk/benefit and cost/benefit analysis in presumptive stage I sarcoidosis showed that observation of a patient with bilateral hilar lymphadenopathy (BHL), presenting without symptoms and with normal physical examination is absolutely justified [75]. Estimates based on the US incidence rates of sarcoidosis came to the following conclusions: if 33,000 persons with asymptomatic BHL underwent mediastinoscopy, 32,982 (99.95%) would be diagnosed with sarcoidosis I, eight with tuberculosis, nine with Hodgkin′s disease, and one with non-Hodgkin′s lymphoma. The benefit of the avoidance of two additional deaths due to the late diagnosis of malignant lymphoma would be highly offset by the number of complications: 407 patients would require hospitalization, 204 would experience major morbidity, and the costs would be 100–200 million US dollars [75]. In another classical study of 100 consecutive patients with BHL, >95% of asymptomatic individuals with BHL and normal physical examination had sarcoidosis [49]. Malignancies were the cause of sarcoidosis in 11 of 100 patients, and all were symptomatic. Therefore, histological confirmation may not be needed in asymptomatic patients who have symmetric BHL. However, when the BHL is asymmetric, massive or associated with large paratracheal enlargement, biopsy confirmation is strongly advised.

In patients with the classical Löfgren′s syndrome, biopsies are usually not necessary. If a Gallium (^{67}Ga) scan is available, the simultaneous demonstration of a lambda pattern (*i.e.* ^{67}Ga uptake in bilateral hilar and right paratracheal lymph nodes) and a panda pattern (uptake in parotis and lacrimal glands) may be sufficient for diagnosis, but the sensitivity of this combination for sarcoidosis is low, only 13–48% [76, 77]. A CD4/CD8 ratio in BAL >3.5 may support the diagnosis of sarcoidosis. The Kveim-Siltzbach test is no longer available in most countries due to availability of tissue, difficulties in standardizing and validating the preparation, and risks of transmission of infective diseases.

Additional investigations

At the initial diagnostic evaluation, a number of tests are strongly recommended as routine procedures for all patients (table 3) [2]. Pulmonary function tests only have a modest correlation with the chest radiograph. They are even important in patients without pulmonary signs and symptoms to provide a baseline for detection of improvement or deterioration of lung involvement during the further course of the disease. Only 20% of patients with stage I disease show abnormalities in pulmonary function tests, compared with 40–70% in the other radiographic stages [55]. The

Table 3. – Recommended tests for initial evaluation of sarcoidosis

Type of evaluation
History (occupational and environmental exposure, symptoms)
Physical examination
Postero-anterior 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

most sensitive tests are the diffusion capacity and the vital capacity tests. As well as a restrictive impairment, an obstructive lung function pattern is seen in up to 30% of patients, and bronchial hyperreactivity is present in ~25% of patients. Blood testing is performed to exclude hypercalcaemia and significant hepatic, renal, or haematological involvement. Routine ophthalmological investigation, including an initial slit lamp examination, is obligatory in all patients in order to exclude a clinically silent uveitis.

Chest CT is not routinely needed. In some patients (according to the author's experience, ~30% of patients), high-resolution CT (HRCT) is indicated for the following reasons: atypical clinical and/or chest radiographic findings; a normal chest radiograph but a clinical suspicion of the disease; suspected complications of lung disease, such as bronchiectasis, aspergilloma, pulmonary fibrosis, and traction emphysema; or a superimposed infection or malignancy.

Apart from hilar and mediastinal adenopathy [78], the characteristic findings of sarcoidosis on HRCT are nodular infiltrates with a bronchovascular and subpleural distribution, thickened interlobular septa, architectural distortion, and conglomerate masses originating from coalescence of nodules in the perihilar, peribronchovascular or subpleural regions. Less common findings are honeycombing, cyst formation and bronchiectasis, and ground-glass opacities or alveolar consolidation. In a similar manner to the conventional chest radiographic findings, lung CT does not correlate well with the functional impairment.

Specific investigations are needed if extrapulmonary sarcoidosis is suspected. These have been discussed in the Organ manifestations section.

Assessment of activity

A long list of laboratory and cell biological markers have been discussed as potential indices of active disease [29, 79–81], either in serum (*e.g.* ACE, lysozyme, neopterin, soluble IL-2-receptor, soluble intracellular adhesion molecule (ICAM)-1, IFN-γ) or in BAL fluid (*e.g.* high lymphocytes, activation marker expression on T-cells, CD4/C8 ratio, macrophage TNF-α release, collagenase, procollagen-III-peptide, vitronectin, fibronectin, hyaluronan). However, none of them can be recommended for routine assessment, perhaps with the exception of serum ACE [82]. The serum ACE only has a limited value in diagnosing sarcoidosis, but it is useful in monitoring the course of disease. Serum ACE is elevated in 40–90% of patients who have clinically active disease. The likely sources of the circulating enzyme are activated epithelioid cells and macrophages at sites of inflammation. Thus, elevated serum ACE levels probably reflect the total body granuloma burden and do not necessarily reflect disease activity in the lungs. They seem to correlate broadly with the number of organs involved and the number of extrapulmonary sites. The magnitude of the initial ACE levels has no prognostic significance and the initial levels are no different between patients who deteriorate and those who improve. After initiation of treatment, serum ACE levels can be helpful in monitoring the treatment effect, since increased serum 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 [18].

At present, the best way to assess the activity of sarcoidosis is still through clinical activity. This is based on the mode of onset, the worsening or persistence of symptoms, and the presence of skin lesions, in combination with changes in chest radiography and lung function tests, with or without treatment.

Natural history and prognosis

The clinical course is highly variable in sarcoidosis, with a tendency for the disease to wax and wane, either spontaneously or in response to therapy. One characteristic feature of sarcoidosis is the high rate of spontaneous remission, globally seen in 60–70% of patients, whereas a chronic course is seen in only 10–30%, depending on geographical and ethnic differences [2, 48, 58, 66, 83–85]. The prognosis is best in acute onset disease, *e.g.* Löfgren's syndrome. Severe extrapulmonary manifestation (*e.g.* heart, central nervous system, liver) is seen at initial presentation in only 4–7% of patients, but this percentage increases with longer disease duration. Permanent sequelae will be experienced by 10–20% of patients. Sarcoidosis can generally be considered as a benign disease with a good prognosis. Sarcoidosis-related mortality is low: only 1–5% of patients die from their disease, most frequently from respiratory insufficiency, neurosarcoidosis or cardiac involvement. Larger series show that 30–50% of all patients require treatment with corticosteroids at some time in their disease course [2, 58, 66]. Several clinical features have been associated with a chronic or progressive course (see table 4) [2, 58, 86].

Many studies have shown that the chest radiographic stages provide useful prognostic information. In fact, no modern biological marker in serum or BAL has been proven to better the conventional chest radiographic staging system in this respect. Spontaneous remission occurs in [2, 84–86]: stage I in 55–90%; stage II in 40–70%; stage III in 10–30%;

Table 4. – Adverse prognostic factors in sarcoidosis

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

and stage IV in 0–5%. These remissions are usually seen after 1–3 yrs. Those patients who spontaneously remit or stabilize show late relapses in only 2–8% of cases [87–89]. Failure to regress spontaneously within 24 months predicts a chronic or persistent course.

The clinical follow-up investigations should include physical examination, chest radiography, serial lung function measurements, and other organ-specific tests if specific organs are involved. For stage I disease, initial follow-up every 6 months is usually adequate; more frequent evaluation (every 3–6 months) is advised for stage II, III, or IV sarcoidosis. All patients should be monitored for a minimum of 3 yrs after therapy is discontinued. Subsequent follow-up is not required unless new or worsening symptoms develop, or extrapulmonary sites are involved. By contrast, patients with persistent, stable disease should be followed over a long period of time, sometimes indefinitely. This also applies to patients with serious extrapulmonary involvement. Patient surveillance needs to be more vigilant after corticosteroid-induced remissions because of the high rate of relapse in this context, ranging from 14–74% (table 5) [48, 84, 87–90]. A recent study showed that there were no relapses if patients remained asymptomatic for 3 yrs after prednisone withdrawal [90].

Treatment

The appropriate treatment has not been well defined for all patients. Because of the variable course of sarcoidosis and the fact that the majority of patients undergo spontaneous remission, indications for therapy are still controversial and the optimal dose and duration of corticosteroids has not been adequately studied in randomized, prospective trials.

Extrapulmonary involvement

Systemic corticosteroids are clearly indicated for life- or sight-threatening organ involvement, *i.e.* cardiac or central nervous disease, or ocular disease not responding to topical therapy. Other indications for therapy include persistent hypercalcaemia, persistent renal dysfunction, severe hepatic dysfunction with portal hypertension or icterus, palpable splenomegaly or evidence of hypersplenism, severe fatigue and weight loss, dysfiguring skin lesions, or chronic myopathy [2, 66, 86].

Table 5. – Intervals and duration of follow-up for sarcoidosis

Stage I disease: every 6 months
Other stages: every 3–6 months
Follow-up for a minimum of 3 yrs after therapy is discontinued
If radiograph has normalized for 3 yrs, subsequent follow-up is not routinely required

Follow-up needs to be more vigilant after corticosteroid-induced remissions than after spontaneous remission.

Pulmonary sarcoidosis

Although the overall effectiveness of corticosteroids in changing the long-term outcome of sarcoidosis is unclear, it is well known that corticosteroids provide acute symptomatic relief and reverse organ dysfunction in patients with symptomatic pulmonary disease. It is obvious that treatment of the cause of sarcoidosis is not possible due to unknown aetiology. The aim of treatment can only be to prevent irreversible loss of function of the involved organs and to improve symptoms, if they are severe and affecting the patient's quality of life. Obviously, the natural course of the disease, *e.g.* the time point when the natural disease activity resolves by the elimination of the causative agent, cannot be influenced by corticosteroids. Most physicians feel that progressive symptomatic pulmonary disease should be treated. It is less clear whether persistent pulmonary infiltrates or mildly abnormal lung function require therapy. Indications for observation are asymptomatic patients who have normal lung function and patients who have minimal, well-tolerated symptoms and only mild, functional abnormalities, until they experience disease progression [2, 88]. This approach is supported by two recent studies, as outlined here.

HUNNINGHAKE *et al.* [88] performed a prospective study of 91 previously untreated patients with sarcoidosis, in which they limited the use of corticosteroids to patients that had objective evidence of recent deterioration in lung function or serious extrapulmonary disease. According to these criteria, 36 were treated with corticosteroids and 55 were observed without therapy. Of these, only eight deteriorated, eventually required corticosteroids and responded to this therapy. Of the 36 patients who were treated with corticosteroids, 20 remained stable and 16 improved clinically.

In the British Thoracic Society study [87], 58 sarcoidosis patients who, in the first 6 months after entry to the study, neither required prednisolone for symptoms nor showed radiographical improvement, were randomly allocated at 6 months to receive either long-term steroid treatment for $\geqslant$18 months, or were treated only selectively if later symptoms developed or lung function deteriorated. In the long-term treatment group, vital capacity improved from an initial value of 89% predicted to a final value of 99% pred. Importantly, in the selective treatment group, vital capacity remained stable, from 89–92%. On average, there was no deterioration in lung function. In addition, only six of 31 patients in the selective treatment group required therapy during follow-up because of symptoms or deterioration of lung function. The author believes that the message from this study is to wait and treat only if symptoms develop or lung function deteriorates.

For pulmonary sarcoidosis, the initial prednisone dose is generally 20–40 mg·day^{-1}: higher doses may be needed for cardiac or neurological sarcoidosis. The dose is slowly tapered to 5–10 mg·day^{-1} over 2–3 months. Alternate day treatment using equivalent total dosages is also effective in maintaining improvement and may decrease the side-effect of hypothalamic

suppression, but not the side-effects of osteoporosis and cataract formation. Treatment should be continued for a minimum of 12 months [2, 91]. Patients with Löfgren's syndrome do not require therapy with corticosteroids because their symptoms usually respond well to nonsteroidal anti-inflammatory drugs. Patients need to be followed for relapse after dose reduction or discontinuation of therapy. Some patients who have repeated relapses may require indefinite therapy.

Alternative drugs

Several cytotoxic agents have been used to treat patients requiring long-term corticosteroid therapy and suffering from major side-effects. Usually, these drugs are combined with corticosteroids and are used in order to lower the dose of steroids, but in some selected cases they may be given as single therapy. On the basis of safety and efficacy, methotrexate (10–25 mg·week^{-1}) and azathioprine (100–150 mg·day^{-1}) are the preferred agents [92–96]. Both have minimal-to-no carcinogenicity with the doses used in sarcoidosis. Cyclophosphamide and chlorambucil should be reserved for refractory cases (table 6) [2].

The antimalarial drugs chloroquine and hydroxychloroquine have been used as first-line drugs for lupus pernio, nasal sarcoidosis, other disfiguring sarcoid skin disease, and hypercalcaemia [97–99]. A recent report indicated the efficacy of chloroquine and hydroxychloroquine in the treatment of neurosarcoidosis after failure of corticosteroid therapy or unacceptable side-effects with corticosteroids [100]. The response rates are higher with chloroquine than with hydroxychloroquine, but hydroxychloroquine is less toxic and may be used for prolonged periods without retinal damage, making it the preferred drug to chloroquine [99, 100]. Chloroquine treatment is best limited to a 6-month period. Recently, chloroquine has also been shown to be effective in chronic pulmonary sarcoidosis [101].

There is anecdotal experience that suggests that pentoxyfylline is beneficial when used alone or with corticosteroids in the treatment of sarcoidosis [102]. This is probably due to its inhibitory effect on alveolar macrophage TNF-α release [103]. Until further study results become available, pentoxifylline therapy still has to be considered as experimental. Thalidomide may be considered as another corticosteroid-sparing option in the treatment of sarcoidosis [104]. Cyclosporine has been shown to have no clinical effectiveness for pulmonary sarcoidosis, despite experimental evidence that suggests that it suppresses the T-helper cell activity in the lungs [105, 106].

With the availability of specific antagonists against TNF-α in the treatment of rheumatoid arthritis, this approach may also be considered in the future for the rare cases of chronic sarcoidosis, refractory to corticosteroids and other immunosuppressive and cytotoxic agents.

Topical corticosteroid therapy

Topical therapy with corticosteroids can be sufficient for some patients with skin sarcoidosis, nasal involvement, iritis/uveitis, or airway disease. Inhaled corticosteroids may reduce symptoms in endobronchial sarcoidosis, such as cough and airway hyperreactivity. The role of inhaled corticosteroids in the treatment of parenchymal pulmonary sarcoidosis is still uncertain. Several recent studies have shown that this therapy has some benefits, but the effects are modest and generally involved groups of patients with mild disease and good prognosis [107, 108]. Other studies failed to show clinical efficacy [109, 110]. In a recent study of inhaled fluticasone in adults with stable sarcoidosis, there was no improvement in any physiological outcome measure [111].

Associated conditions and complications

Patients who have advanced fibrocystic sarcoidosis may develop bronchiectasis and mycetomas. Both complications may give rise to life-threatening haemoptysis [66, 112]. Surgical resection and embolization of the bronchial arteries have been reported as helpful in selected cases. Systemic antifungal agents are not recommended since no clinical trials have demonstrated efficacy. Usually, haemoptysis is the result of associated bronchiectasis and bronchitis, and responds to conservative therapy with bedrest, cough suppression, antibiotics and increased corticosteroid

Table 6. – Alternative drugs for sarcoidosis

Toxicity*	Drug and dosage			
	Methotrexate 10–25 mg·week^{-1}	Azathioprine 50–200 mg·day^{-1}	Cyclophosphamide 50–150 mg·day^{-1}	Hydroxychloroquine 200–400 mg·day^{-1}
Nausea	1	2	3	1
Mucositis	2	1	1	0
Haematological	1	2	3	0
Teratogenic	2	1	3	0
Carcinogenic	0	1	3	0
Other	Liver, lung	Liver	Bladder	Retinal

*: 0=none; 1=minimal; 2=occasional problem; 3=significant problem; it may be necessary to adjust the dosage or to use other agents.

doses [66]. In these cases, maintenance low-dose corticosteroids may be helpful in minimizing repeated episodes of haemoptysis.

In end-stage pulmonary sarcoidosis and cor pulmonale, supplemental oxygen, diuretics and bronchodilators for obstructive impairment are indicated. Lung and other organ transplantation has been successfully performed in sarcoidosis [113, 114]. Although recurrent sarcoid lesions are common in the lung allograft, fortunately, this is not clinically or radiographically relevant. Survival is comparable to other lung transplant recipients [114].

Osteoporosis is a potential complication in patients who are treated with corticosteroids. Since sarcoidosis may induce hypercalciuria and hypercalcaemia by increased endogenous vitamin D production, patients should be monitored closely when vitamin D or calcium is supplemented for osteoporosis prevention [115]. Calcitonin and bisphosphonates have been shown to reverse steroid-induced osteoporosis in sarcoidosis patients [116].

Outlook

In the past 2 decades, many advances have been made in gaining a better understanding of the pathogenesis, the incidence and prevalence of the disease, and some genetic factors, which may define patients with a distinct phenotype and prognosis. Making a diagnosis with less invasive procedures is also understood.

However, many issues of clinical management and understanding of disease development in individual patients are still unclear. The new millennium will probably provide answers to the following questions: whether there is an early test to predict disease progression and prognosis; if there are less toxic therapies than corticosteroids or cytotoxic agents; which genetic factors increase susceptibility to the disease; how genes modify the expression of the disease; what mechanisms lead to persistent disease and development of fibrosis; and which agent(s) cause sarcoidosis.

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