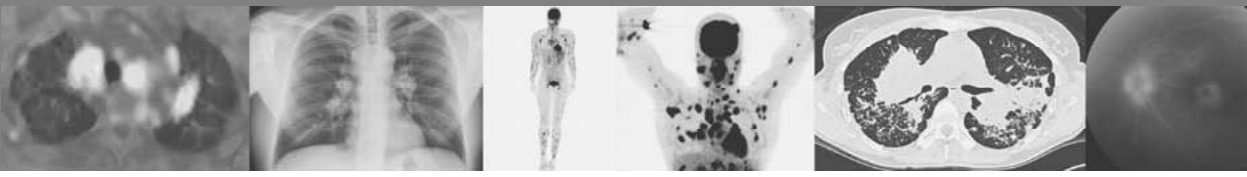
Chapter 1

General introduction



Demographical and prognostic characteristics in sarcoidosis

Sarcoidosis is a multisystemic disease characterized by cellular immunity activity with formation of noncaseating granuloma in various organ systems.[1] The disease affects people of all ages, but most commonly those in the third to fourth decade of their lives.[2] Sarcoidosis is prevalent throughout the world, but the incidence and phenotype differs according to specific regions and race. The highest annual incidence of sarcoidosis has been observed in northern European countries (5 to 40 cases per 100,000 people).[3] In a study that was performed in the USA, African Americans had about a threefold higher age-adjusted annual incidence (35.5 per 100,000) compared with Caucasians (10.9 per 100,000).[4]

Löfgren's syndrome is the most frequent type of presentation in the Scandinavian countries and is defined by the presence of acute onset symptoms with fever, arthralgias, erythema nodosum, and bilateral hilar lymphadenopathy (see Figure 1.1 and 1.4b). In Japan, cardiac involvement and uveitis are more common.[5]

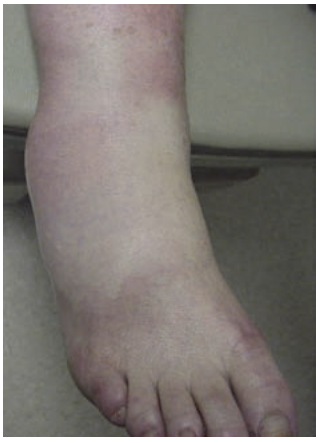


Figure 1.1 Ankle arthritis and erythema nodosum in a patient with Löfgren's syndrome.

In general, sarcoidosis has a beneficial prognosis. Remission occurs within 3 years of the diagnosis for more than half of the patients, and within a decade for two-thirds with few or no consequences.[5] The remaining one-third of the patients suffers from persistent disease, leading to significant organ impairment. Less than 5% of patients die of sarcoidosis, death is usually the result of cardiac or neurological involvement, or of respiratory failure due to pulmonary fibrosis.[2,6] Löfgren's syndrome usually carries a good prognosis, being self-limiting within six months after initial presentation in the majority of the patients. Patients characteristics like black race, lupus pernio, bone involvement, advanced pulmonary disease are associated with a chronic course of the

disease (Table 1.1).[7-10] The differences in incidence and phenotype complicate comparing and executing studies concerning prognosis and treatment effect, since patient populations are heterogeneous. Several scoring systems have been used to assess the level of disease and clinical outcome. In order to standardize the clinical outcome description of patients with sarcoidosis, a novel clinical outcome score was recently developed by a task force of the World Association of Sarcoidosis and Other Granulomatous Diseases (WASOG).[11]

Table 1.1 Characteristics associated with worse prognosis.[12]

Age >40 at onset
African American
Requirement for steroids
Extrapulmonary involvement
Cardiac
Neurological (except isolated cranial nerve palsy)
Lupus pernio
Splenomegaly
Hypercalcemia
Osseous disease
Pulmonary involvement
Stage III–IV chest radiograph
Pulmonary hypertension
Significant lung function impairment
Moderate to severe dyspnea on presentation
Neutrophilia in bronchoalveolar lavage fluid at presentation

Clinical presentation

The clinical presentation is highly variable. The disease primarily affects the lungs and the lymphatic system, but virtually every organ system can be involved (Table 1.2).[1] The most common symptoms include fatigue, respiratory symptoms like coughing or dyspnea, and symptoms related to extrapulmonary involvement.[5]

Pulmonary involvement

Involvement of the pulmonary parenchyma and mediastinal lymphadenopathy is present in approximately 90% of the sarcoidosis patients; hence the pulmonologist is often the prominent physician in the management of the disease. However, since any organ may be affected, a multidisciplinary approach is needed in a substantial part of the patients.[1,13] The various diagnostic tools are discussed below.

Table 1.2 Historical estimate of the prevalence of organ involvement in sarcoidosis.[1]

Organ involvement	% of the patients
Mediastinal lymphadenopathy	95-98
Lung	>90
Liver	50-80
Spleen	40-80
Eye	20-80
Extrathoracic lymphadenopathy	20-30
Skin	25-30
Central nervous system	10-15
Small fiber neuropathy	25-70
Muscle	10-75
Heart (symptomatic)	5-15
Bone (symptomatic)	1-10
Kidney	2-5

Fatigue

Despite the fact that fatigue is a common problem (with a reported prevalence of 30-90%) and a clear hallmark in sarcoidosis patients that affects quality of life, it still remains underestimated and poorly inderstood.[14] De Vries et al. found no relationship between fatigue in sarcoidosis patients and a number of clinical variables, including lung function, metabolic variables, laboratory parameters of inflammation and T-cell activation and granuloma formation.[14] A recent study showed that, although exercise intolerance and muscle weakness are frequent problems in sarcoidosis, fatigue was not predicted by the presence of these and other clinical characteristics.[15] The fatigue assessment scale (FAS) has been shown to be an easy, reliable and valid scale for assessing fatigue in sarcoidosis patients.[16] When evaluating sarcoidosis patients suffering from fatigue, it is important to exclude disorders that may interact with fatigue in sarcoidosis, i.e. obstructive sleep apnea syndrome, hypothyroidism and depression.[17-19]

Exercise capacity

A substantial number of patients with symptomatic sarcoidosis display exercise intolerance (45%), as well as muscle weakness (prevalence rates of 12–27%). Patients with impaired peripheral muscle strength are more fatigued and demonstrate impaired lung function test results, six-min walk distance (6MWD), and quality of life (QoL) compared with patients without reduced peripheral muscle strength.[15] Another cause of exercise intolerance can be the presence of pulmonary hypertension, which occurs in 6-23% of patients at rest and in more than 40% of patients during exercise.[20] Pulmonary hypertension complicates pulmonary sarcoidosis more frequently in advanced parenchymal disease and significantly worsens prognosis.[5]

Neurosarcoidosis

The prevalence of clinical involvement of the central nervous system is estimated to be about 5-15% in patients with sarcoidosis.[21] It is a serious and commonly devastating complication of sarcoidosis and can present in many different ways, like cranial neuropathy, cerebral sarcoid lesions, papilledema, psychiatric symptoms, aseptic meningitis, hydrocephalus, seizures, spinal sarcoidosis, peripheral neuropathy, and small fiber neuropathy.[21-23] Furthermore, patients may present with evidence of pituitary or hypothalamic dysfunction.[24] In patients with confirmed active systemic sarcoidosis, neuroimaging studies, especially magnetic resonance imaging (MRI), and electrophysiological studies can support the diagnosis of neurosarcoidosis. Tissue confirmation remains the gold standard for unconfirmed cases or for patients with a history of sarcoidosis but with no evidence of disease activity.[21]

Uveitis

Ocular involvement is present in 30-60% of patients with sarcoidosis and can be a source of considerable morbidity if not properly diagnosed and treated.[25] This eye disease may occur in the absence of apparent systemic involvement or may be the main site of disease without significant clinical disease elsewhere.[26] Therefore, routine slit-lamp and funduscopic examination is necessary. Patients who present with only ocular findings pose a unique challenge, as establishing a definitive diagnosis with intraocular biopsy can be associated with significant morbidity.[25] International criteria for the diagnosis of ocular sarcoidosis were reported by the committee of the first international workshop on ocular sarcoidosis (IWOS).[26] Inflammatory patterns can be classified as anterior (iris and/or ciliary body), intermediate (vitreous) or posterior (retina, choroid) uveitis. Anterior uveitis is the most common manifestation, occurring in 65% of patients with ophthalmologic involvement. Acute anterior conjunctivitis can occur in Löfgren's syndrome and generally has a favorable prognosis. In contrast, chronic anterior uveitis is more notable for causing ocular morbidity.[27] Posterior segment involvement is reported to occur in nearly 30% of the patients with ocular sarcoidosis.[2] This type of uveitis should be considered vision-threatening and can be accompanied by central nervous system involvement.[2,27] Inflammation of all three ocular compartments (anterior, intermediate, and posterior) or panuveitis is a poor prognostic risk factor.[28]

Cardiac involvement

Cardiac sarcoidosis is a rare but potentially fatal manifestation of sarcoidosis. Clinically apparent cardiac involvement is present in approximately 5% of the patients, but much higher frequencies of myocardial granulomas have been reported in autopsy studies.[2,29] Cardiac sarcoidosis is manifested clinically as a cardiomyopathy with loss of muscle function or tachyarrhythmias and bradyarrhythmias (palpitations, syncope,

and death). In every patient with sarcoidosis, an electrocardiogram (ECG) should be perfomed.[1] If symptoms like palpitations or conduction abnormalities on the ECG are present, further evaluation, including cardiac MRI or fasting cardiac fluorine-18 fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET), is warranted.[2,30,31] Active sarcoid lesions and their response to steroid treatment may be better detected by ^{18}F-FDG PET, whereas fibrotic lesions might be shown more clearly by MRI or other nuclear myocardial perfusion imaging.[32] The value of metaiodobenzylguanidine scintigraphy (MIBG) will be discussed in chapter 2.

Cutaneous involvement

Cutaneous involvement is common (occurring in 25-35% of patients with sarcoidosis) and often overlooked or misinterpreted, given the variability of the lesions.[2] Special attention should be given to scars and tattoos, since these are preferential sites of granulomatous inflammation. Lupus pernio is more common in women and is associated with chronic disease and extrapulmonary involvement.[33] In contrast, erythema nodosum is mainly present in patients with Löfgren's syndrome. Detection of changes in cutaneous lesions can be of great value for the clinical assessment of inflammatory activity, since these sites are easily accessible without the need for technical investigations (Figure 1.2).

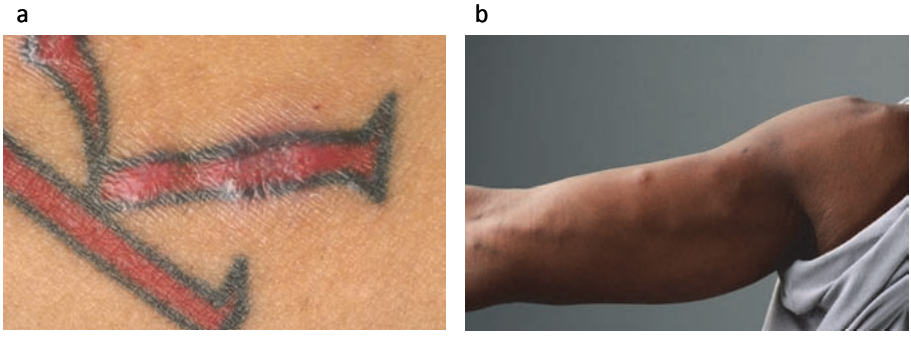


Figure 1.2 **a**. Sarcoid cutaneous involvement in a tattoo, **b**. Multiple subcutaneous nodules located on the upper extremity of a patient with sarcoidosis.

Pathogenesis

Although advances in understanding the immunopathogenesis of sarcoidosis have been made, the cause of sarcoidosis remains unclear. The development of sarcoidosis is probably the end result of immune responses to various ubiquitous environmental triggers in genetically susceptible individuals.[2]
Granulomas, the hallmark of sarcoidosis, are compact, centrally organized collections of macrophages and epithelioid cells encircled by lymphocytes. The presence of granuloma is not specific for sarcoidosis, but can also occur in other interstitial lung diseases, e.g. hypersensitivity pneumonitis, berylliosis and pulmonary Langerhans cell histiocytosis. Granuloma formation and maintenance is initiated by the presence of CD4+ T-cells that interact with the major histocompatibility complex class II molecules on antigen presenting cells.[34] These activated CD4+ T-cells differentiate into type 1 helper T (Th1)-like cells and secrete predominantly interleukin-2 (IL-2) and interferon-γ (IFN-γ), augment macrophage tumor necrosis factor-alpha (TNF-α) production, and amplify the local cellular immune response.[2] IL-2 acts as a local growth factor for T-lymphocytes, whereas INF-γ enhances the accessory and cytotoxic function of T-cells and regulates the secretion of other lymphokines.[5] TNF, IL-12 and IL-18 induce IFN-γ production and enhance T-cell cytotoxicity.[35] Due to this immunological response the cells organize into granuloma. Granulomatous inflammation can spontaneously resolve or persist with the development of chronic disease. If ongoing antigen presentation is present, an increased production of macrophage-generated cytokines, e.g. transforming growth factor-β, favor the development of fibrosis.[5] However, the exact mechanisms are still largely unknown. Recently, Sweiss et al. identified several significant associations between disease sub-phenotypes and serum levels of TNF-α and type I IFN, which were distinct in different ancestral backgrounds.[36] These results suggest that different cytokines may be more important in a particular group of patients with sarcoidosis. Figure 1.3 shows a schematic presentation of granuloma formation in sarcoidosis.

The ACCESS (A Case Control Etiologic Study of Sarcoidosis) study identified several environmental exposures modestly associated with sarcoidosis risk, including insecticides, agricultural employment, and microbial bioaerosols.[17] Occupational studies have shown positive associations with service in the U.S. Navy, metalworking, firefighting, the handling of building supplies and man-made mineral fibres.[2,37] Furthermore, Mycobacteria and Propionibacteria have been identified as possible causative agents.[38]

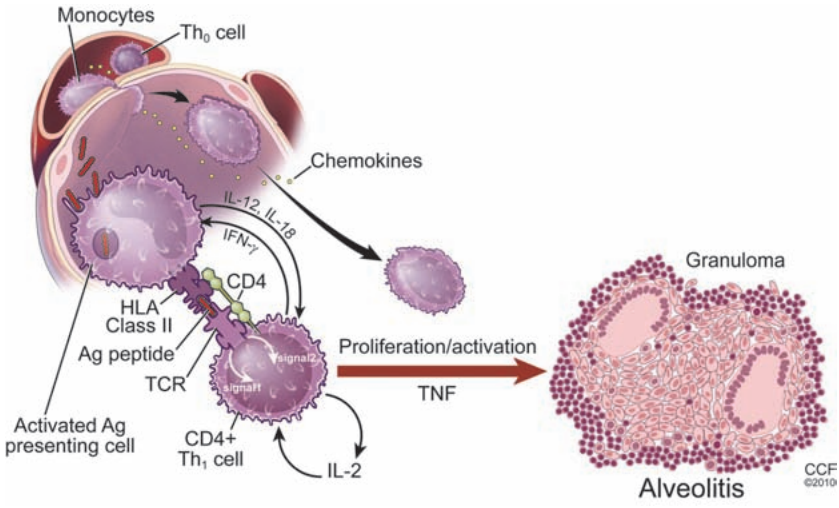


Figure 1.3 A schematic presentation of granuloma formation in sarcoidosis.
Th= T-helper; Ag= antigen; HLA: human leukocyte antigen; IFN-γ= interferon-gamma; IL= interleukin; TCR: T-cell receptor; TNF= tumor necrosis factor (adapted from Baughman[48]). Hypothetical model of the pathogenesis of sarcoidosis. An antigen induced antigen-specific, Th1-mediated granulomatous inflammation with production of Th1 cytokines (IFN-γ, IL-2). The efficiency of antigen processing, antigen presentation and cytokine release is probably under genetic control; evidence strongly supports a role for macrophage HLA and butyrophilin-like 2 (BTNL2) alleles in sarcoidosis susceptibility and phenotype. Granuloma formation is set in motion by activated macrophages and T-cells along with other effector cells (e.g. fibroblasts) under the regulatory influence of local cytokine production. Removal of the antigen allows transforming growth factor-beta (TGF-β) to downregulate the immune response. Alveolar macrophages activated in the context of a predominant Th2 response appear to stimulate fibroblast proliferation and collagen production, leading to progressive fibrosis.[2]

Familial clustering of sarcoidosis has been demonstrated.[39] Patients stated that they had siblings or parents with sarcoidosis five times more often as control subjects.[17] Human leukocyte antigens (HLA) are cell surface proteins that are essential for immune recognition and function. Reports suggest that specific HLA genotypes confer a predisposition to the disease phenotype rather than to susceptibility.[2,40,41] For example, HLA-DQB1*0201 and HLA-DRB1*0301 are strongly associated with acute disease and a good prognosis, whereas the haplotype HLA-DRB1*1501/HLA-DQB1*0602 was found to be associated with a chronic course and severe pulmonary sarcoidosis.[41-44] The presence of butyrophilin-like 2 (BTNL2) variant alleles is associated with an increased risk of progressing to persistent pulmonary sarcoidosis,[45] besides an increased risk to develop sarcoidosis[45,46], although the independence of the BTNL2 association with sarcoidosis was questioned in another study.[47]

Diagnosis

The diagnosis of sarcoidosis is supported by a compatible clinical and radiographic presentation together with histological evidence of noncaseating granulomas on biopsy. In Löfgren's syndrome, a feasible diagnosis of sarcoidosis can be made on the clinical picture, without the need for a biopsy.[1]

Treatment

Most patients require no treatment, but several pharmacologic options exist for those patients with an indication for therapy. Nevertheless, none of these drugs are curative. Non-steroidal anti-inflammatory drugs (NSAIDs) can be efficient for symptom relief in patients with arthralgia/arthritis. Topical treatment can be very effective in cutaneous involvement. Decisions on whether to start systemic immunosuppressive treatment or not are based on clinical features, like organ dysfunction or, in selected cases, symptoms that affect quality of life, i.e. severe cutaneous involvement that does not respond to topical treatment. The drug of first choice is prednisone, limited evidence is available for the use of other immunosuppressive drugs like methotrexate, azathioprine, leflunomide or hydroxychloroquine and, more recently, TNF-α inhibitors.[2,49-58]

Assessment of inflammatory activity

In general, assessment of inflammatory activity is vital in the management of sarcoidosis, and is especially necessary to monitor the course of sarcoidosis and guide therapeutic strategies.[57,59,60] The presence of inflammatory activity means that the disease has not yet come to a rest, that there is still ongoing T-cell and macrophage inflammation and granuloma formation, with the potential that the disease may progress, whereas the absence of inflammatory activity means that the disease has come to a rest and will likely not progress.[59] However, in sarcoidosis, activity should be distinguished from severity. Activity in sarcoidosis does not necessarily indicate a progressive course, a fatal prognosis, or the need for medical treatment.[61] The presence of inflammatory activity can be regarded as certain in case chest radiography (CXR) findings or lung function test results provide evidence of disease progression and in patients with acute, symptomatic sarcoidosis.[62,63] Nevertheless, assessment of inflammatory activity in sarcoidosis patients with unexplained persistent disabling symptoms remains a challenge for clinicians.

The assessment of inflammatory activity by clinical and radiographic features can be complicated as organ involvement beyond the scope of the used diagnostic tools,

might be missed. Symptoms like arthralgia or fatigue can be nonspecific and difficult to objectify.[12,14,15] Furthermore, symptoms like coughing and dyspnea might be related to ongoing inflammatory activity as well as to end-stage disease, i.e. pulmonary fibrosis. It is important to be informed about the presence or absence of inflammatory activity in those patients as fibrosis itself is irreversible. In general, patients with fibrosis without ongoing inflammatory activity are thus supposed not to benefit from immunosuppressive treatment.[12] A technique, able to evaluate the presence of inflammatory activity per organ system, is therefore desirable.

Laboratory parameters

Inflammatory activity is characterized by ongoing T-cell and macrophage activity and granuloma formation, reflected by an increase in serological markers of inflammatory activity, i.e. angiotensin-converting enzyme (ACE), soluble interleukin-2 receptor (sIL-2R) and neopterin, or abnormal glucose metabolism.[53,59,63-69]

ACE

In sarcoidosis, ACE is mainly produced by activated granuloma cells (epithelioid cells).[2] The reported sensitivity and specificity of ACE for diagnosing sarcoidosis is moderate, even if corrected for genotype (insertion/deletion polymorphism).[70,71] In general, serum ACE levels are higher in clinically active compared with inactive disease, and correlate with disease extent to a certain degree. However, low ACE serum levels do not exclude activity of sarcoidosis, especially in chronic disease or when immunosuppressive therapy is used.[59,72] Furthermore, there is insufficient evidence that ACE levels can predict disease outcome. It should be noted that measurement of ACE levels is not useful in patients taking ACE-inhibitors.

sIL-2R and neopterin

IL-2 plays an important role in controlling T-cell proliferation.[73] After binding to the IL-2 receptor on T-cells, it forms the IL-2 receptor complex.[74] IL-2R immunoassays can measure a soluble part of the IL-2R (sIL-2R). sIL-2R is elevated in patients with active sarcoidosis.[62,65,67] It has been shown to correlate with the number of CD4+ T-lymphocytes in bronchoalveolar lavage (BAL) fluid, extrapulmonary disease and respiratory functional impairment.[64,67] It may have prognostic value in sarcoidosis.[62,65,66] Neopterin represents activation of the monocyte/macrophage system, and is found to be increased in active and progressive disease as well.[66]

C-reactive protein

C-reactive protein (CRP) is an acute-phase protein. Measurement of plasma or serum CRP levels can be useful to differentiate inflammatory from non-inflammatory conditions.[75] In sarcoidosis, CRP levels appeared to be elevated, especially in acute

disease, but the mean CRP concentrations of patients with stable or progressing disease (indicating severe disease) did not differ significantly from those in healthy controls, in contrast to sIL-2R.[62] In another study, the predictive value of CRP for the presence of respiratory functional impairment was much lower than that of sIL-2R.[64]

These serological inflammatory markers are not specific for sarcoidosis. CRP levels can be elevated by a wide range of inflammatory processes.[75] Elevated ACE levels can be found in other granulomatous diseases like tuberculosis and silicosis, and also in hyperthyroidism.[76] sIL-2R levels can be increased in patients with malignant lymphomas, tuberculosis, HIV, rheumatoid arthritis, and lupus erythematosus.[77-81] However, specificity is of less importance as these markers are not used for establishing the diagnosis of sarcoidosis, but only for the assessment of inflammatory activity.
Higher levels of other serological inflammatory markers like chitotriosidase, lysozyme, nuclear regulatory factor-kappaB (NF-κB), and the glycoprotein KL-6 have been observed in patients with active sarcoidosis, but these markers require further validation before they can be used in clinical practice.[82-84]
Elevated calcium levels can be found in both serum and independently in the urine as a result of increased production of 1,25-dihydroxyvitamin D3 in the granuloma and thus can be considered as a marker of granuloma activity, but with a low sensitivity.[2,59] If hypercalcemia is present, other causes of this feature like hyperparathyroidism should be considered. Liver-test abnormalities are present in 10-25% of all sarcoidosis patients, but liver involvement is usually clinically silent.[2,85] Moderate and severe liver-test abnormalities seemed to be associated with more advanced histopathological disease.[85]

Lung function tests

Deterioration of lung function is regarded as an indicator of disease activity in sarcoidosis.[59] A wide spectrum of lung function abnormalities can be present, including an obstructive pattern, restriction, a mixed obstructive and restrictive ventilatory effect, and a decreased diffusion capacity of the lungs for carbon monoxide (DLCO).[86] Airway hyperreactivity occurs in 5-83% of patients.[87] Abnormal lung function tests, especially forced expiratory volume in one second (FEV1), forced vital capacity (FVC), and DLCO are traditionally used as an indication for treatment.[59] Baseline lung function tests are not related to the probability of disease progression and cannot distinguish between reversible granulomatous lesions and irreversible fibrotic changes.[59] In 80% of sarcoidosis patients presenting with abnormal spirometric findings, values return normal within 2 years.[88] No obvious correlation between lung function test results and CXR findings exists, although prominent lung restriction occurs especially in patients with CXR stages III-IV (this staging system is described below).[59,86] Due to the wide-ranging variety of possible lung function

abnormalities in sarcoidosis, depicting a single lung function test as primary measure of change is difficult. In an individual patient, repeated performance of complete lung function testing, including spirometric and plethysmographic volumes as well as DLCO measurement, seems most appropriate for longitudinal assessment.[86] This shows that defining a single lung functional primary endpoint in pharmacological studies is problematic. Furthermore, assessment of disease activity through lung function tests requires evidence of progression between two measurements and so does not reflect that actual state.

Bronchoalveolar lavage

Disease presentation or activity at the time the BAL is performed as well as the smoking status is crucial for interpretation of individual BAL fluid analysis results.[89] In sarcoidosis, the majority of patients have an increased number of lymphocytes and a normal amount of eosinophils and neutrophils.[89,90] The relative proportion of lymphocytes can be somewhat higher in clinically active disease (range 20-80%, mean around 40%) versus clinically inactive sarcoidosis (mean lymphocytes 30%). There is considerable overlap in lymphocytes between active and inactive disease, and BAL may be normal in 10-15% of patients.[91,92] Lymphocytosis in BAL fluid has not shown to be predictive of more progressive pulmonary disease. To date, an increase in the number of neutrophils in BAL fluid was found to be associated with an unfavorable outcome.[62,93] The analysis of other inflammatory mediators like cytokines and chemokines in BAL fluid may have potential clinical application in the future.[94-96] BAL has no role in the detection of responsiveness to therapy.[86]

Chest radiography

Between 85 and 95% of sarcoidosis patients have abnormalities on chest radiographs. According to the Scadding radiographic staging system, five stages of radiographic abnormality can be recognised: stage 0 (normal CXR), stage I (bilateral hilar lymphadenopathy (BHL)), stage II (BHL and parenchymal abnormalities), stage III (parenchymal abnormalities without BHL) and stage IV (advanced lung fibrosis with evidence of honeycombing, hilar retraction, bullae, cysts and/or emphysema) (Figure 1.4).[1,97] Patients initially present with CXR stage 0 in 5-15%, stage I in 45-65%, stage II in 30-40%, stage III in 10-15% and stage IV in 15-25%, respectively. As mentioned before, there is no strong relationship between CXR stages and lung function test results. However, in general, patients with a lower radiographic stage are more likely to experience resolution of symptoms and CXR abnormalities.[86] A recent study showed that survival is significantly decreased in CXR stage IV patients and that 75% of the fatalities are directly attributable to respiratory causes.[98]

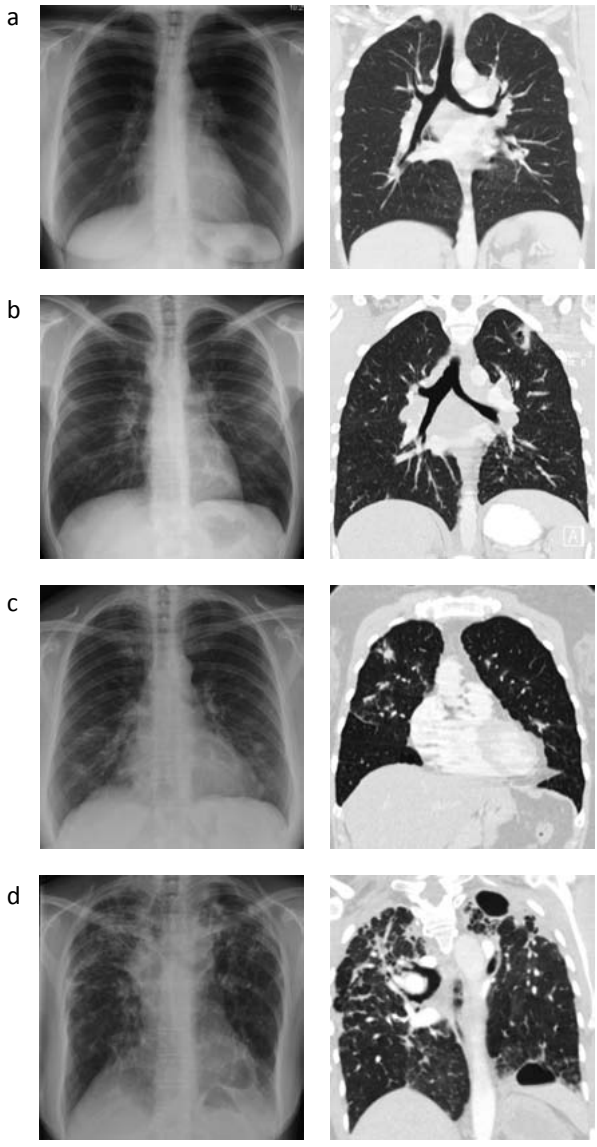


Figure 1.4 Chest radiographic staging system in sarcoidosis.

a. Stage I : CXR (left) and coronal high-resolution computed tomography scan (HRCT; right) showing bilateral hilar lymphadenopathy, without parenchymal abnormalities.

b. Stage II: CXR (left) and coronal HRCT image (right) showing both lymphadenopathy and parenchymal abnormalities (nodular and reticulonodular opacities).

c. Stage III: CXR (left) and coronal HRCT image (right) showing parenchymal abnormalities without hilar lymphadenopathy.

d. Stage IV: CXR (left) and coronal HRCT image (right) showing signs of lung fibrosis with hilar retraction and architectural distortion of the pulmonary parenchyma.

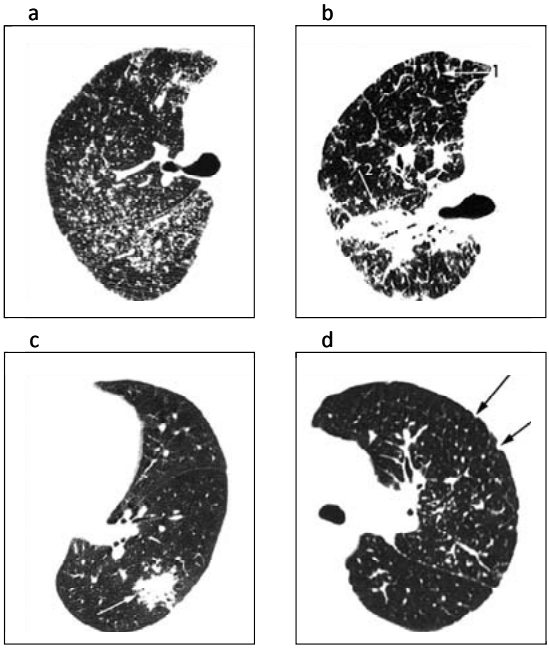


Figure 1.5 HRCT images of a sarcoidosis patient to illustrate the use of the semiquantitative HRCT scoring system that has been described by Oberstein et al.[112] Adapted from Drent et al.[107]
a. Intra-parenchymal nodules. **b.** Septal and nonseptal lines (*1*→); Thickening or irregularity of the bronchovascular bundle (*2*→). **c.** Parenchymal consolidation (including ground-glass opacifications). **d.** Focal pleural thickening (*arrows*).

High-resolution CT

The high-resolution computed tomography (HRCT) uses short scanning times and thin collimation, making it possible to view lung parenchyma in detail and detect abnormal changes of the lung parenchyma at an early stage.[99-104] HRCT appearances in sarcoidosis are characterized by peribronchovascular thickening and perilymphatic nodular distribution. Other common patterns are: enlargement of the mediastinal and hilar lymph nodes, ground-glass opacification, parenchymal consolidations, and signs of fibrosis (architectural distortion as shown by distortion of the airways and blood vessels, irregular distortion of the septal and intralobular lines, retraction of the hila and fissures, cystic formation and traction bronchiectasis).[99,103,105] Follow-up CT scan studies in patients with pulmonary sarcoidosis showed that nodular opacities represent potentially reversible findings.[105,106] In contrast, differentiation between fibrotic and granulomatous components in parenchymal consolidations cannot be made based on HRCT findings. The above-mentioned follow-up CT scan studies also

showed that cystic air spaces and architectural distortion are irreversible findings, irrespective of treatment.[105,106] Due to pre-existing major abnormalities, radiological features are frequently of limited value for assessment of inflammatory activity in sarcoidosis patients with fibrotic disease.

The presence and extent of parenchymal abnormalities on HRCT appeared to correlate with functional impairment in sarcoidosis.[107-111] To achieve a reliable comparison of results, a standardized (semi-)quantitative estimation of abnormal findings on HRCT is mandatory. In clinical practice, it is important that the chosen HRCT score is complete, valid, reproducible, easy to learn, and rapid.[107] Intra- and inter-reader reliability of a semiquantitative HRCT scoring system that was adapted from one previously described by Oberstein et al.[112] (Figure 1.5; see also Chapter 5 and 6) demonstrated good agreement.[107] This total HRCT score, but not the radiographic stage, appeared to predict the presence of respiratory functional impairment in the same study. Furthermore, this scoring system was related to various biochemical biomarkers of disease activity and the number of neutrophils in the BAL fluid.[93,112]

^{18}F-FDG PET

^{18}F-FDG PET is used to detect high glucose metabolism in malignancies or infectious foci and to explain fever of unknown origin.[68,69,113] The glycolysis of inflammatory cells is enhanced when these cells are stimulated. This is mainly attributable to the high number of glucose transporters present in these cells and also to the enhanced affinity of these transporters for glucose.[69] The uptake of ^{18}F-FDG follows the same pathway as glucose, but once it has entered the cell, it is phosphorylated by hexokinase enzyme to ^{18}F-2'-FDG-6 phosphate. This cannot be further degraded via the glycolysis pathway nor can it easily undergo dephosphorylation by glucose-6-phosphatase.[114] It is proposed that inflammatory cells such as activated macrophages and lymphocytes at the site of inflammation are responsible for the accumulation of FDG.[114-116]

PET has been shown to be a very sensitive technique for the assessment of inflammatory activity in sarcoidosis by detecting and quantifying the degree of inflammatory and granulomatous reactions that occur in the lungs and elsewhere in the body.[63,117-119] In patients with proven sarcoidosis, the extent of involvement and quantification of inflammatory activity can be more accurately assessed by ^{18}F-FDG PET than with ^{67}Gallium scintigraphy.[118-120] Apart from its value for assessment of inflammatory activity, ^{18}F-FDG PET is therefore also useful to identify occult and reversible granulomas in patients with sarcoidosis (Figure 1.6).[117] In addition, PET has several practical advantages over ^{67}Gallium scintigraphy as it is less time-consuming, the inter observer agreement is higher and the radiation exposure lower.[119]

Somatostatin receptor scintigraphy (SRS), most frequently performed with Indium-111, has also been shown to reveal sarcoidosis sites.[121] A study by Lebtahi et

al.[122] suggested that, compared with gallium scintigraphy, SRS appeared to be accurate and contributed to a better evaluation of organ involvement in sarcoidosis patients, especially those treated with corticosteroids. However, it missed 40% of the known extrathoracic sites. To our knowledge, the literature includes no data on potential advantages of SRS over PET-scanning in the detection of granulomatous sites in patients with proven sarcoidosis.

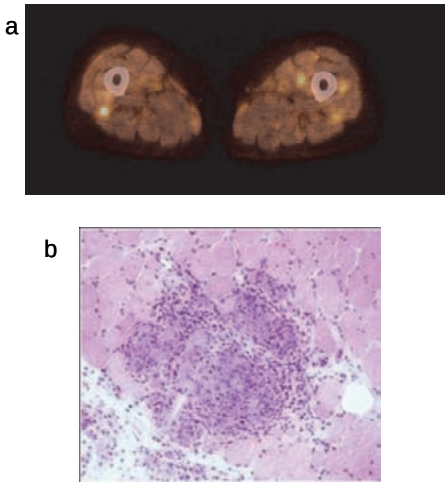


Figure 1.6 **a.** PET/CT image of a sarcoidosis patient showing multiple foci with increased FDG-uptake in the muscles of the lower extremities. **b.** Noncaseating granuloma present in a biopsy obtained from the left quadriceps muscle of the patient with sarcoidosis.

Scope and aims of the study

In current clinical practice, serological parameters, i.e. ACE, CRP, sIL-2R, and neopterin, in combination with clinical indices like lung function parameters and radiological findings are most commonly used to assess inflammatory activity and disease severity in sarcoidosis. Sometimes however, patients suffer from disease related persistent disabling symptoms, and no signs of inflammatory activity could be detected with these routine investigations. Inflammatory activity assessment in these cases remains a challenge for clinicians, as absence of evidence does not mean evidence of absence. The management of patients with unexplained persistent disabling symptoms, therefore, requires reliable and clinically useful markers of inflammatory activity. The aims of the studies presented in this thesis were to evaluate the relationship between the currently available markers of inflammatory activity, and the relationship between these markers and parameters of disease severity in sarcoidosis patients. The studies included patients with sarcoidosis who had had unexplained persistent disease-related disabling symptoms for at least one year and were referred to a tertiary care center in the Netherlands. In addition, we assessed the response of inflammatory signs and clinical characteristics to treatment with adalimumab in sarcoidosis patients with refractory chronic uveitis.

Chapter 2 provides an overview of the knowledge about and limitations of the use of metaiodobenzylguanidine (MIBG) scintigraphy in cardiac and pulmonary diseases. **Chapter 3** reports on the assessment of the presence of inflammatory activity using fluorine18-fluorodeoxyglucose positron emission tomography (PET) in 89 sarcoidosis patients with unexplained persistent disabling symptoms, and evaluates the association between PET findings and serological inflammatory markers. **Chapter 4** describes the prevalence and distribution pattern of bone and bone marrow involvement as detected by PET/CT in 94 sarcoidosis patients with a positive PET. **Chapter 5** evaluates the association between the severity of the pulmonary involvement and PET activity in 95 persistently symptomatic sarcoidosis patients. **Chapter 6** makes an attempt to develop a prediction rule that can be used to identify persistently symptomatic sarcoidosis patients for whom there is a high probability that PET will show the presence of inflammatory activity. **Chapter 7** presents the results of a prospective case series that included 26 sarcoidosis patients with refractory uveitis. The study evaluated the effect of adalimumab on intraocular inflammatory signs and other relevant clinical manifestations (lung function, serological inflammatory parameters, and fatigue) of sarcoidosis. **Chapter 8** provides a summary of the findings presented in this thesis and argues their implications. Finally, directions for future research are discussed.

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