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Prognostic Factors in Sarcoidosis

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1. Introduction

Sarcoidosis is a multisystem disorder of unknown etiology. Inflammation mediated by lymphocytes of Th1 phenotype leads to formation of non-caseating granulomas, consisting of epithelioid and multinucleated giant cells. In the majority of patients it affects intrathoracic lymph nodes and lungs, but all organs may be involved (ATS, ERS, WASOG Statement on Sarcoidosis). The overall prognosis is good, and in about 60 % of all cases the disease regresses spontaneously. In the rest of patients, sarcoidosis is a chronic disease, sometimes showing up with relapses, which often follow withdrawal or dose reduction of steroids (Gottlieb et al., 1997; Neville et al., 1983; Scadding, 1961). In about 10-15 % it slowly progresses to lung fibrosis, which is the major cause of death, affecting less than 1 % of patients in Europe and up to 5% in North America. The immunopathological concepts on sarcoidosis describe mechanisms leading to induction of granuloma formation, mechanisms responsible for prolongation and sustaining of inflammation, and mechanisms responsible for fibrosis (the latter are the worse recognized). Although the etiology of sarcoidosis is unknown, it is generally acknowledged that the disease develops in genetically predisposed subjects who were exposed to unidentified (presumably inhaled) antigen(s). This unidentified "sarcoid factor" has the ability to persist in the intracellular milieu of macrophages, which results in the production of cytokines responsible for transformation of Th0 to Th1 cells. In response, lymphocytes produce a variety of cytokines which conversely stimulate macrophages and induce their transformation to granuloma cells. There is premise to speculate that the ability to eliminate the antigen from the intracellular environment is *sine qua non* of complete and definitive remission (Grunewald, 2002). Although mechanisms regulating these processes are not known, this knowledge seems to be critical for understanding the pathogenesis of persistent and progressive sarcoidosis.

Selection of patients at higher risk of lung fibrosis or other unfavorable outcomes at the early stages of disease is a hard task for a physician. There are no objective tests which would be helpful in this matter. Some prognostic factors important for a certain ethnic group may be useless in another. The most important question is whom to treat, and how to treat to achieve the best final cost/effect ratio.

Statement on Sarcoidosis, a document published by ATS, ERS and WASOG in 1999, lists a number of clinical factors of prognostic significance. These factors include: lupus pernio, chronic uveitis, age of onset >40 yr, chronic hypercalcemia, nephrocalcinosis, black race, progressive pulmonary sarcoidosis, nasal mucosal involvement, cystic bone lesions, neurosarcoidosis, myocardial involvement and chronic respiratory insufficiency. Different prognostic factors of real or potential clinical relevance will be discussed in this chapter.

2. Radiology

2.1 Chest X-ray

In the 50's, two radiologists, Nitter and Wurm (DeRemee, 1983; Nitter, 1953; Wurm et al, 1958) proposed a three-stage classification system based on chest X-ray (1-enlarged lymph-nodes alone; 2- enlarged lymph-nodes plus parenchymal changes; 3- parenchymal changes without signs of intrathoracic lymph-nodes involvement). Today, a five-stage radiological classification is in use. It is ascribed to Scadding, who added stage 0 (for patients with normal chest X-ray) and stage IV (for patients with signs of irreversible lung fibrosis) (Scadding, 1961).

Scadding was one of the first to report on the influence of radiological stage on the long-term prognosis. He found that after > 5-years follow-up, 84% of patients with initial radiological stage I experienced complete radiological remission and even in the situation when hilar enlargement persisted, patients presented only with mild symptoms or were asymptomatic. In stage II, radiological remissions were observed in 58% of patients, and in stage III (clearly separated from stage IV) this percentage was as high as 43% (in later studies the chance of spontaneous remission in this stage was estimated at 10-20%). Of note, there were no remissions in the group with radiological signs of fibrosis (stage IV), and only in this group did sarcoidosis-related deaths occur. Many authors further confirmed the adverse relationship between III/IV radiological stage and worse long-term prognosis. Reich, in his meta-analysis (Reich, 2002), estimated that sarcoidosis mortality is 4.8% in referral centers and 0.5% in population-based settings, and is attributed to stage III/IV radiological stage. Viskum and Vestbo (1993) reported on their results of a 27-year follow-up study of 254 sarcoidosis patients, showing that radiological stage III was related to excess mortality. The authors also proved that early clearance of chest X-ray is a good prognostic factor.

Staging based on the chest X-ray remains the main clinico-radiological classification of sarcoidosis, but limitations are evident, and include: low sensitivity in determining small lymph nodes and tiny parenchymal shadows, problems with differentiation between parenchymal granulomatous infiltrations from signs of fibrosis, and relatively low levels of agreement between examiners (Baughman et al, 2009). Advantages of chest X-ray-based classification are: low costs, low radiation dose per one examination, general availability of a chest X-ray, and paradoxically, low sensitivity (what allows a clinician a first-glance diagnosis).

2.2 Computed tomography

Contrast-enhanced CT scans may be helpful in diagnosis of hilar/mediastinal lymphadenopathy, differentiating lymph nodes from vessels, and in all cases where there is a threat of malignancy. However, the presence of adenopathy, in contrast to parenchymal changes, is not an adverse risk factor for unfavorable outcome. Therefore, high resolution computed tomography (HRCT), which enables a precise estimation of the extent of pulmonary involvement and a detailed qualitative description of parenchymal changes, may be more useful as a tool for disease severity evaluation. Drent et al (2003) proposed a simple classification of HRCT signs based on the presence and extent of the most frequent findings in sarcoidosis patients: thickening or irregularity of the bronchovascular bundle, intra-parenchymal nodules, septal and nonseptal lines, and parenchymal consolidation, including ground-glass opacifications. The authors found that patients with higher total

HRCT scores were more likely to have worse lung function parameters and abnormal gas exchange. They found HRCT superior to chest X-ray in depicting respiratory disability. Thickening of bronchovascular bundle and septal/nonseptal lines were especially linked to worse spirometric values and gas exchange parameters. Interestingly, "clear" lung parenchyma did not rule out abnormal gas exchange. Other authors confirmed that patients with extensive bronchovascular bundle thickening are at increased risk of developing irreversible bronchial obstruction (Handa et al., 2006). Another group of authors evaluated HRCT initially and after a mean follow-up period of 7.4 years in 40 patients and concluded that predominant small and multiple large nodules in the majority of cases disappeared or decreased in size, whereas ground-glass opacities and consolidations evolved into honeycombing. In addition, significant functional and respiratory impairment accompanied this evolution (Akira et al, 2005). Abehsera et al (2000) defined three CT signs of definitive lung fibrosis in patients suffering from stage IV disease: bronchial distortion, honeycombing and linear patterns. Emphysematous pattern is rare, but should be added to the list of possible irreversible radiologic changes in stage IV sarcoidosis (Akira et al, 2005). These and other reports (Malaisamy et al, 2009) indicate that small disseminated nodules (the most frequent finding in lung parenchyma of sarcoidosis patients) and also confluent nodes are potentially reversible, whereas others may represent fibrosis at different stages of evolution. Therefore, HRCT scans may be useful in predicting the outcomes of patients with pulmonary sarcoidosis.

3. Lung function tests and other measures of functional disability

3.1 Lung function tests

The risk of lung function impairment is greater in patients with a more advanced radiological stage. However, the disparity between radiological signs of parenchymal involvement and lung function tests results is quite common in sarcoidosis. It has been estimated that normal spirometry (vital capacity) may be seen in up to 80% of patients with stage I and 35% of patients with stage II and III (Winterbauer & Hutchinson, 1980]. A restrictive pattern of ventilatory impairment occurs in about 30-50% of all sarcoidosis patients. Atypical to other interstitial lung diseases, a significant proportion of patients present with bronchial obstruction. In one series from Japan, the percentage of patients with FEV_1/FVC <70% was 8.8, and was associated with radiographic stage IV, higher age, smoking, and thickened bronchovascular bundles on CT (Handa et al., 2006). Other authors reported a much higher incidence of bronchial obstruction (Kieszko et al., 2004; Sharma & Johnson, 1988). Harrison et al. estimated that bronchial obstruction at different levels of the bronchial tree is the most common functional abnormality in sarcoidosis (Harrison et al., 1999). Bronchial obstruction may be independent of the parenchymal involvement, and results from the predilection to peribronchial and endobronchial formation of granulomas (Kieszko et al., 2004; Sharma & Johnson, 1988). Its frequency increases with the increasing radiological stage (Lamberto, 1985).

Initial lung function impairment has an obvious impact on long-term prognosis. In one study (Viscum & Vestbo, 1993) patients with FEV_1 <50% of predicted had an increased mortality risk of 4.2, compared to patients with FEV_1 >80%. Bronchial obstruction (FEV_1/FVC<70%) increased the mortality risk to 1.9. Also, patients with lung restriction defined as TLC<80% of predicted value had an increased mortality risk (RR=2.6). Other authors in a long-term follow-up study (Mañá et al., 1996) found that initial FVC<80% of predicted value is a strong predictor of persistent disease (RR=2.17).

Regardless of the evident negative prognostic value of impaired lung function test results at the initial evaluation, it was shown by many authors that in some patients these abnormalities are potentially reversible after long term observation. Approximately 80% of subjects had an improved or stable FVC and FEV_1 after two years follow-up. Interestingly, changes in FVC alone were found unreliable as descriptors of pulmonary status, as they did not fully correspond to radiological changes or symptoms (Judson et al., 2003). Although bronchial obstruction (FEV_1/FVC <70%) is a strong predictor of unfavorable outcome, it was shown that when it is attributed merely to bronchial sarcoid granulomas, it may be completely or partially reversible with immunosuppressive treatment in >70% of patients (Lavergne et al., 1999). Bronchial obstruction related to other mechanisms like bronchial scarring, airway distortion secondary to interstitial fibrosis, or other mechanisms may be burdened with a much worse prognosis.

3.2 Diffusion capacity

Diffusion capacity for carbon monoxide (DLCO) is a measure frequently used to estimate the severity of lung parenchymal involvement. DLCO disturbances may result from deprivation of gas exchange area, increase of barrier thickness or ventilation-perfusion mismatching. According to general understanding, DLCO is a very sensitive marker and its decrease may herald the development of irreversible fibrosis. It may be especially useful in monitoring of disease progression or regression (spontaneous or resulting from treatment). It was shown to be a good predictor of gas exchange abnormalities at exercise; moreover, from the two components of DLCO (alveolar membrane diffusing capacity and pulmonary capillary blood volume), the effect was rather related to the "membrane" component (Lamberto, 1985). However, the vascular component may also be important, as DLCO<60% predicted was proven to be a strong predictor of pulmonary hypertension in sarcoidosis (Bourbonnais & Samavati., 2008). Unfortunately, DLCO also has some limitations. DLCO may represent transient gas transfer impairment, especially in patients with stage I or II with low grade parenchymal lung disease, where gas exchange may be altered by reversible mechanisms. Dunn et al. reported that DLCO of idiopathic pulmonary fibrosis (IPF) patients was significantly lower comparing to sarcoidosis patients; regardless the comparison was performed in patients with the same level of lung volume impairment. This observation suggests that diffusing capacity may not be a sensitive indicator of pulmonary pathology in sarcoidosis since lung volume can be altered independently of abnormalities in the diffusing capacity (Dunn et al., 1988).

3.3 Six-minute walk test

The six-minute walk test (6MWT) is a simple test used to assess the exercise capacity in patients suffering from different respiratory and heart diseases. Changes in exercise capacity may be due to such factors as lung function, cardiac status, respiratory and skeletal muscle strength. Its role in the clinical assessment of sarcoidosis is still growing. In one series of patients, six-minute walk distance (6MWD) <400 m was documented in >50% of patients (Baughman et al., 2007). Several factors were associated with reduced results of the test, including FVC, oxygen saturation with exercise and self-reported respiratory health (Baughman et al., 2007). Some authors suggest that distance-saturation product (DSP), which is a result of the 6MWD multiplied by the lowest oxygen saturation, better reflects the functional status in patients with sarcoidosis, and it was shown to correlate with female gender, pulmonary function parameters (especially FEV_1), partial pressure of oxygen, Borg

dyspnea score, lung fibrosis on HRCT, pulmonary hypertension and systemic therapy (Alhamad et al., 2010). The impaired exercise tolerance in sarcoidosis may be explained at least in part by reduced peripheral muscle strength (Marcellis et al., 2011). Patients with sarcoidosis-associated pulmonary hypertension walk shorter distances and desaturate during the 6MWT. Desaturation <90% during the test was shown to be a very strong predictor of sarcoidosis-associated pulmonary hypertension (Bourbonnais & Samavati, 2008).

Alveolar-arterial oxygen pressure gradient ($P(A\text{-}a)O_2$) during exercise may be useful in selection of patients demanding immunosuppressive treatment. Of note, impaired gas exchange during exercise also occurred in some patients with normal spirometry and DLCO. Good correlation was observed with radiological staging (Kollert et al., 2011).

4. Bronchoalveolar lavage (BAL) cells

The typical finding in sarcoidosis is an increase of BAL lymphocyte count, displayed by 80-90% of patients at the time of initial diagnosis. The lymphocyte percentage is an activity marker, and an average increase in active disease reaches 30-60%, but higher percentages are also observed. About 60% of patients have a CD4/CD8 ratio above 3.5, which is highly specific for sarcoidosis. Sensitivity of both high BAL lymphocyte percentage and CD4/CD8 ratio is however, unacceptably low (Costabel, 1998).

It was shown that lymphocytic alveolitis is an unstable feature, because in 75% of initial high intensity alveolitis the lymphocyte BAL content spontaneously dropped and in 12% of patients with initial low-grade alveolitis it spontaneously reverted to high intensity alveolitis after approximately 6-month follow-up observation. In the latter case, the increase of BAL lymphocyte percentage was frequently followed by the deterioration in at least one lung function parameter at the next 6-month follow-up examination (Keogh et al., 1983). According to the majority of authors, high BAL lymphocytes are not connected with worse long-term prognosis, and may even determine a subpopulation of patients with evidently better prognosis (Tahanovich et al., 2003). BAL lymphocytes >35 % predicted a good response to treatment, as indicated by an increase in FVC value in >90% of patients, whereas patients with low-intensity alveolitis deteriorated in 50% of cases, regardless of the treatment (Hollinger et al., 1985). Many authors did not find any differences in BAL lymphocytes content between subgroups of different prognosis as defined by radiological stage, chronicity or other factors (Vidal Serrano et al., 2005; Ziegenhagen et al., 2003); whereas some authors report higher intensity alveolitis in patients with stage I comparing to stage III (Danila et al., 2008; Verstraeten et al., 1990). Follow-up studies clearly show the lack of negative prognostic value of high lymphocyte content in BAL. The recovery of lymphocytes in lavage fluid had no prognostic value for persistent disease in the over two-year follow-up studies (Bjermer et al., 1988; Verstraeten et al., 1990).

High content of CD4 lymphocytes or high CD4/CD8 ratio in BAL are more relevant markers of activity comparing to total lymphocyte BAL percentage (Costabel, 1998). Patients who improved radiologically had higher numbers of CD4 cells and higher CD4/CD8 ratio comparing to patients who deteriorated or remained unchanged (Verstraeten et al., 1990). Also, patients with higher CD4/CD8 at initial diagnosis responded better to treatment (Baughman et al., 1984; Płodziszewska et al., 2000).

The detailed characterization of BAL lymphocyte subpopulations by flow cytometry may be promising in description of patients with worse prognosis. For instance, lymphocytes with

higher expression of CD95, an apoptotic molecule (Fas), were found in unexpectedly high amount on the surface of BAL lymphocytes from patients with progressive sarcoidosis (Ozdemir et al., 2007). Increased number of Th17 cells may be predictive for progressive sarcoidosis and may help in selecting patients under increased risk of lung fibrosis (Facco et al., 2011). As yet, lymphocytes subpopulations other than CD4 and CD8 are not in everyday use in clinical practice.

Several authors report on the possible prognostic value of BAL neutrophils. Patients with stage 3 had higher concentrations of BAL neutrophil elastase than patients with stage 1 or 2 (Danila et al., 2008; Peros-Golubcić et al., 2001). The length of disease duration correlated with the lung lavage neutrophil counts (Peros-Golubcić et al., 2001). It was shown that patients with lower neutrophil count in BAL have a greater chance to recover spontaneously (Drent et al., 1999). Ziegenhagen et al reported on significantly elevated percentage of BALF neutrophils in patients with progressive disease, and found that increased percentage of neutrophils in BAL >3% may predict the future necessity of treatment (Ziegenhagen et al., 2003).

Some authors reported on possible prognostic value of increased BALF eosinophils (Danila et al., 2008; Ziegenhagen et al., 2003) and mast cells (Bjermer et al., 1988). Patients with high percentage of neutrophils and eosinophils in BAL fluid more frequently have gas exchange impairment on exercise (Kollert et al., 2011).

5. Laboratory markers

A huge number of biochemical and immunological markers have been evaluated so far in the context of diagnosis, estimation of activity or prognosis. The most frequently used biological materials are serum and BAL fluid, but some new possibilities emerged recently, for instance, exhaled breath condensate (EBC) analysis (Piotrowski et al., 2007; Psathakis et al., 2004). These markers include substances that are directly produced by granuloma cells (angiotensin converting enzyme, ACE) or that result from their metabolic activity (increased serum and urinary calcium due to increased rate of hydroxylation of vitamin D), or acute phase reactants (CRP), or various immunological markers involved in initiation and propagation of granulomatous inflammation (cytokines, soluble receptors, lipid peroxidation products, other mediators).

5.1 Angiotensin converting enzyme (ACE)

Angiotensin converting enzyme is a product of active granuloma cells. It has been the most widely used laboratory marker in sarcoidosis, as it was shown to correlate with the total volume of granulomas within an organism. Unfortunately, it is neither specific nor sensitive. Its serum concentration is elevated only in about 60% of patients with active sarcoidosis (Gupta et al., 1979), and high concentrations were reported in patients with lung diseases other than sarcoidosis (Farber et al., 1980; Studdy et al., 1978). Moreover, its levels may be influenced by polymorphism of the ACE gene (Arbustini et al., 1996). SACE concentrations were proven to correlate with the extent of lung parenchymal infiltrations (Studdy et al., 1980). It was also shown to normalize in response to treatment and to follow spontaneous remissions (Pietinalho et al., 1999; Planck et al., 2003; Studdy et al., 1978; Studdy et al., 1980). It correlates with BAL lymphocytes, although it was shown to be inferior comparing to BAL lymphocyte count in differentiating active from inactive disease (Rossman et al., 1982). Patients with stage I sarcoidosis and low SACE levels seem to have better prognosis than

patients with the same radiological stage and elevated SACE concentrations (DeRemee & Rohrbach, 1984; Krychniak-Soszka & Kuś, 2002). According to some authors, SACE may help to differentiate patients with stable and persistent or progressive disease (Mañá et al., 1996), but other authors do not confirm this observation (Rust et al., 1985; Ziegenhagen et al., 2003). Therefore, it may be concluded that the role of SACE in predicting the course of sarcoidosis is limited.

5.2 Altered calcium metabolism

25-hydroxyvitamin D undergoes 1α-hydroxylation to form more active 1,25 dihydroxyvitamin D, and granuloma cells possess high amounts of 25-hydroxyvitamin D-1α-hydroxylase, responsible for this conversion (Bell et al., 1979). Elevated serum calcium concentrations may be found in about 11% of patients with sarcoidosis, abnormal urinary calcium loss in about 40 % of patients, and nephrocalcinosis in about 10 % [Ianuzzi et al., 2007]. Severe abnormalities in calcium metabolism, like persistent hypercalcemia, may bear serious and sometimes life-threatening consequences and constitute an independent indication to treatment (ATS, ERS, WASOG Statement on Sarcoidosis, 1999). Therefore, hypercalcemia *per se* is a factor which may potentially worsen the prognosis. Altered calcium metabolism is more frequent in patients with more advanced and chronic lung sarcoidosis and in those with extrapulmonary disease (Neville et al., 1983). Also, chronic nephrocalcinosis in the course of sarcoidosis is usually linked to a chronic course and often an unfavorable outcome (Neville et al., 1983).

5.3 Acute phase reactants

Serum C-reactive protein (CRP) is elevated in almost all patients with Löfgren syndrome and is frequently normal in asymptomatic patients and those with more advanced disease (Rothkrantz-Kos et al., 2003; Mert et al., 2007). Therefore it may not be linked to worse prognosis in the crude population of sarcoidosis patients. In chronic sarcoidosis, however, elevated CRP may identify a subpopulation of patients with more extensive and severe disease. It may also be helpful in identifying patients with better response to treatment with the anti-TNF agent, infliximab (Sweiss et al., 2010).

Serum amyloid A (SAA) is another acute phase reactant which is related to HDL-cholesterol. Its diagnostic value in sarcoidosis is similar to CRP (Rothkrantz-Kos et al., 2003), but recent data show its potential role in the pathogenesis of sarcoidosis, as it was shown to be deposited in granuloma cells. This molecule is capable of triggering the release of cytokines through an interaction with toll-like receptor 2 (Chen et al., 2010). This may be one of mechanisms responsible for chronicity of inflammation, but the clinical value of SAA in predicting the chronic course of sarcoidosis is unknown. Patients suffering from sarcoidosis-related fatigue did not have higher concentrations of CRP and SAA in serum (de Vries et al., 2004).

The level of immunoglobulins is elevated in serum (and BAL) in above 50 % of patients (Bergmann et al., 1997). Circulating immune complement binding complexes are detected in 67% of patients (Schoenfeld et al. 1994). Hyperglobulinemia was shown to influence the persistence of activity over time in one study (Maña et al., 1996).

5.4 Other immunological markers

Neopterin is a product of macrophages, and its serum concentration may reflect the level of macrophage stimulation. The exact biological role of this pro-inflammatory mediator is

unclear. Among others, it was shown to induce intercellular adhesion molecule (ICAM-1) in type 2 pneumocytes, and it may contribute to prolongation of the inflammatory response (Hoffman et al., 1999). Serum neopterin level is higher in patients with progressive sarcoidosis compared to patients with stable disease or Löfgren syndrome (Ziegenhagen et al., 2003). In patients who experienced spontaneous regression, the concentration of neopterin decreased with time (Planck et al., 2003).

Soluble receptor of IL-2 (sIL2R) is a marker of T-cell activation, and is a reliable activity marker in sarcoidosis. Similarly to neopterin, it was elevated in progressive rather than in stable disease or patients with Löfgren syndrome (Ziegenhagen et al., 2003). It was shown to be the most reliable activity marker when compared with hsCRP (hs for high sensitivity), SACE and SAA (Rothkrantz-Kos et al., 2003). The same authors reported that only 7 of 31 untreated patients with low sIL2R values, but 8 of 11 with high sIL2R values needed treatment in follow-up observation (meaning that 73 % of patients with high values, but only 23% of patients with low sIL2R had less favorable outcome). Both sIL2R and neopterin were increased in sera of patients who needed treatment in a follow-up, and this effect was especially strongly pronounced in a subgroup of patients with acute symptoms, indicating a rare subpopulation of severe acute sarcoidosis at high risk of progression (Prasse et al., 2008).

Another product of inflammatory cells is a mucin-like high molecular weight glycoprotein KL-6. It was shown to be superior to other markers, such as SAA, sIL2R, lysozyme, and SACE in predicting chronic course. It was the best to reflect the level of lymphocytic alveolitis and was the only marker which predicted a progressive parenchymal disease (Miyoshi et al., 2010). In another study, KL-6 in serum inversely correlated with lung function parameters and DLCO, and highest concentrations were associated with persistence and progression of parenchymal infiltrates (Janssen et al., 2003).

A huge number of other immunological markers were evaluated in the context of prognosis and outcome in sarcoidosis. Tumor necrosis factor (TNF)-α is produced spontaneously by lung macrophages and T cells at the site of inflammation, whereas peripheral cells are quiescent (Müller-Quernheim et al., 1998; Rastogi et al., 2011). It is one of the key cytokines for granuloma formation, and its importance was documented by the effectiveness of anti-TNF agents in the treatment of refractory sarcoidosis. In one study, low TNF-α levels in BAL fluid were shown to better predict poor outcome, rather than high concentrations. In this context, TNF-α seems to behave like an acute phase reactant, as the highest concentrations were detected in patients with Löfgren syndrome, and were accompanied by high concentrations of IL-6 and higher percentage of lymphocytes in BAL (Tahanovich et al., 2003). Other authors do not confirm such a relationship. Ziegenhagen et al. (2002) found exaggerated release of TNF-α from BAL macrophages in corticosteroid-resistant sarcoidosis. Other authors have recently shown reduced expression of Th1 cytokines, including TNF-α, in HLA-DRB1*0301 positive patients characterized by excellent prognosis (Idali et al., 2006).

Interferon (IFN)-γ is another Th1 related cytokine, indispensible for granuloma formation (Müller-Quernheim et al., 1998). It is a key cytokine in sarcoid inflammation. Treatment with interferons may induce sarcoidosis (Papaioannides et al., 2004). Its BAL concentrations are correlated to CD4/CD8 ratio (Kopiński et al., 2007). BAL levels of IFN- γ and IL-12 (a strong stimulant of IFN production) were significantly higher in sarcoidosis patients comparing to systemic sclerosis or IPF, diseases of much worse prognosis (Meloni et al., 2004). A group of IFN-inducible chemokines may be responsible for sustaining the inflammation. These cytokines are called CXCR3 ligands due to a common affinity to

CXCR3 receptor, include monokines induced by IFN-γ – MIG (CXCL9), IFN-γ-inducible protein 10 – IP-10 (CXCL10) and IFN-γ-inducible T-cell α chemoattractant - ITAC (CXCL11). These chemokines may be elevated in BAL or serum of sarcoidosis patients, and the trend towards higher concentrations in patients with more advanced radiological stage in opposition to patients with Löfgren syndrome was noticed (Busuttil et al., 2009; Nishioka et al., 2007). Potential usefulness of these cytokines as prognostic markers merit further study.

Interleukin (IL)-18 is a monocyte/macrophage derived cytokine, playing an important role in induction of Th1 response. It is a very strong IFN-γ inducing factor. IL-18 level was the highest in plasma of patients with disease progression, in patients with lung interstitial changes and patients with extrapulmonary manifestation of the disease (Kieszko et al., 2007). Chitotriosidase, an enzyme secreted by activated macrophages and involved in defense against chitin-containing pathogens, was shown to correlate with the extent of lung changes, as assessed by radiological staging (Grosso et al., 2004). Higher serum vascular endothelial growth factor (VEGF) concentrations were found in patients with severe sarcoidosis who deserved treatment and in patients with extrapulmonary sarcoidosis (Sekiya et al., 2003).

Another example of a biological marker of potential prognostic value is tryptase, which was elevated in serum of sarcoidosis patients, and the highest values were detected in subjects with progressive disease (Bargagli et al., 2009). In another study, it was found that patients with positive collagenase activity in BAL are more likely to require therapy, and had worse pulmonary function tests at initial evaluation (Ward et al., 1990).

8-Isoprostane, a product of non-enzymatic peroxidation of arachidonic acid, is elevated in BAL (Montuschi et al., 1998) and exhaled breath condensate (EBC) of patients with sarcoidosis, and a trend towards higher levels was noticed in patients with parenchymal disease. Patients with low concentrations of 8-isoprostane in EBC were more likely to recover early (Piotrowski et al., 2010). These observations, however, have experimental rather than practical value.

The list of agents involved in the pathogenesis of sarcoidosis is very long and almost all may be measured in biological fluids of sarcoidosis patients. Some of them have been evaluated in clinical context as potential markers of activity and some of them have been shown to predict unfavorable outcome. In the majority of cases the knowledge on the potential prognostic value of these agents is based on single reports, and the studied groups were rather small. None of these markers, except for SACE, CRP and parameters of calcium metabolism are used in everyday clinical practice.

6. Extrapulmonary sarcoidosis

Intrathoracic lymph nodes and lungs are involved in above 90% of patients. The frequency of extrapulmonary sarcoidosis is estimated by different authors from few to above 80%, depending largely on geographical location or ethnic origin (ATS, ERS, WASOG, 1999; Ianuzzi et al., 2007). Multiorgan involvement is always connected with chronic and more severe course.

Some locations negatively influence the course due to potential serious disability or possible fatal outcome. Cardiac sarcoidosis and neurosarcoidosis are the best examples. Ocular sarcoidosis is a serious problem as it may insidiously lead to blindness. Rare examples of severe life-threatening extrapulmonary disease are renal and laryngeal sarcoidosis. A severe

complication of sarcoidosis which may influence the outcome is sarcoidosis-related pulmonary hypertension.

Cardiac sarcoidosis is frequently unrecognized, as there is a great disproportion between clinical diagnosis and autopsy findings. This is a dangerous situation as unrecognized cardiac sarcoidosis may lead to sudden death (Reid, 1998). In Europe and North America cardiac sarcoidosis is the second cause of death in sarcoidosis patients. In Japan, where cardiac sarcoidosis is very frequent, it is a primary reason. Cardiac sarcoidosis is listed as one of the cardinal indications for treatment (ATS, ERS, WASOG, 1999). In one study, the survival in most patients with symptomatic cardiac disease was limited to approximately 2 years (Roberts et al., 1977), but may be much better when patients are diagnosed and treated early (Chapelon-Abric et al., 2004). New studies with use of modern diagnostic techniques (MRI, PET) provide evidence of very good prognosis in some asymptomatic patients with minimal changes in the heart (Yazaki et al., 2001).

Also, in the case of neurosarcoidosis, there is a discrepancy between clinical diagnosis and real involvement of the nervous system. Symptoms are frequently mild and unspecific and include headaches, dizziness, vertigo, etc. In about 10 % of cases, magnetic resonance images are normal (Zajicek et al., 1999). Similar to cardiac sarcoidosis, neurosarcoidosis is a cardinal indication for treatment. It is, however, important from the clinical point of view that among the various presentations of neurosarcoidosis, not all have an evidently bad prognosis. Facial nerve palsy, aseptic meningitis, isolated headache and vertigo resolve frequently without sequelae. Definitely worse prognosis is connected with spinal cord disease, optic nerve involvement, epilepsy and intracranial mass (Pawate et al., 2009; Zajicek et al., 1999).

There are several extrapulmonary locations that are not life-threatening but which are statistically associated with chronic and progressive course, and are therefore predictors of poor outcome. Examples are: lupus pernio, chronic uveitis, chronic hypercalcemia, nephrocalcinosis, nasal mucosal involvement and cystic bone lesions (Neville et al., 1983; Panselinas et al., 2010; Stagaki et al., 2009).

7. Symptoms

Löfgren syndrome, which is more frequent in younger patients, consists of arthritis, fever, erythema nodosum in a patient with hilar lymphadenopathy and forecasts a good prognosis. In about 80-90 % of these patients symptoms vanish within 2-8 weeks, and radiological changes disappear within 2 years at the latest (Maña et al., 1996). Recurrent Löfgren syndrome may occur many years after the first episode, but further episodes do not seem to worsen the prognosis (Maña et al., 2003). Erythema nodosum is a good prognostic sign, both for stage I and stage II patients (Krychniak-Soszka & Kuś, 2002). Acute symptoms at the beginning do not, however, guarantee an excellent prognosis, as about 16% of patients presenting with erythema nodosum pursued a chronic course (Neville et al., 1983).

Respiratory symptoms related to severe functional dysfunction have obvious negative prognostic value. But patients with chronic sarcoidosis frequently report non-respiratory and respiratory symptoms not necessarily connected with lung function impairment or other evident causes. The most frequent are fatigue, breathlessness, reduced exercise capacity and arthralgia, and they significantly influence the patients' quality of life (Michielsen et al., 2007). Fatigue is reported by more than 80% of patients with sarcoidosis.

Reduced exercise tolerance and fatigue are also frequent and may be unrelated to radiological stage and the degree of functional impairment (Marcellis et al., 2011).
In patients with chronic sarcoidosis, an asymptomatic course usually occurs in less severely ill patients. For instance, fatigue is more severe in patients with both pulmonary and extrapulmonary disease than in patients with only pulmonary involvement (Gvozdenovic et al., 2008) .
Other chronic symptoms, like loss of weight, sweating, or elevated body temperature, are more frequent in patients with liver involvement, but prognostic value of these symptoms is unknown.

8. Age and gender

8.1 Age

Typically, sarcoidosis is a disease of young adults, with an incidence peak between 20-29 years, and a second "smaller" peak, at least in Caucasians, in patients over 50. The disease is rare in the elderly, and very rare in children. African American patients are usually older at onset. A worse outcome in patients with disease onset >40 years was reported (Romer, 1982, as cited in ATS, ERS, WASOG, 1999). It should be taken into consideration that sarcoidosis spotted in an elderly patient is frequently the result of an asymptomatic disease which had lasted for many years. Co-morbidities, frequent in this age group (including neoplasms), may influence the general prognosis. Self-limiting disease with an acute clinical presentation more typical of younger patients may also be observed in patients over 60. On the other hand, sarcoidosis in children may be systemic, chronic, progressive and recurrent (Baculard et al., 2001; Kendig & Brummer, 1976). Lenner et al. (2002) compared clinical features of patients with disease onset < 50 and > 50 year of age, and did not find significant differences. In conclusion, although older patients deserve more thorough clinical monitoring, the influence of mere age on the course of sarcoidosis is uncertain.

8.2 Gender

Female sex is slightly overrepresented in patients suffering from sarcoidosis. Gender may also influence the clinical presentation of symptoms. For instance, in patients with acute sarcoidosis, erythema nodosum is more frequent in women, while periarticular inflammation of the ankles or ankle arthritis is more prevalent in men (Grunewald & Eklund, 2007). Women suffering from sarcoidosis experience more symptoms, lower quality of life and greater degree of functional impairment (Alhamad et al., 2010; Bourbonnais et al., 2010; De Vries et al., 1999). Women of African-American origin may have greater risk of co-morbities (Westney et al., 2007). Female gender is also associated with higher incidence of coexisting autoimmune disorders (Antonelli et al., 2006). Women with sarcoidosis are over 2 times more frequently treated in hospital than men, however this effect may be limited to black race (Foreman et al., 2006). The analysis of sarcoidosis-related mortality in the US over a period of 20 years revealed an increase in mortality related to an increase in non-Hispanic black females (Swigris et al., 2011). But gender did not predict the need for therapy at 18-24 month follow-up (Baughman et al., 2006). In a large series of patients from Finland and Japan, gender did not influence the rate of spontaneous remissions (Pietinalho et al., 2000). Also in Arabs and Asians, gender did not influence the long-term prognosis (Behbehani et al., 2006). From the cited studies it may be concluded that female gender may be linked to a

worse prognosis, but this effect seems to be influenced by patients' ethnic origin, and is the most visible among African American women.

9. Genetics

The role of genetics in the pathogenesis of sarcoidosis is well acknowledged. It has been supported by occurrence of familial sarcoidosis, differences in the disease incidence between different ethnic groups and race-specific clinical features. It has been well documented that the incidence of sarcoidosis is four times higher among African Americans than among Americans of Caucasian origin. African Americans suffer from more severe disease. Higher incidence of extrapulmonary sarcoidosis, progressive sarcoidosis and sarcoidosis related deaths were reported in this population (Israel et al., 1986, ATS, ERS, WASOG, 1999). Black race is therefore a risk factor of chronic and progressive course (ATS, ERS, WASOG, 1999). In Japanese patients, the extraordinarily high frequency of cardiac and ocular sarcoidosis was reported, but the rate of spontaneous radiological remissions is much higher in this population than in Finnish patients (Pietinalho et al., 2000).

The last two decades has yielded a number of genetic studies in sarcoidosis in the context of disease susceptibility and prognosis. Polymorphisms in HLA class I and II have been the most extensively studied. The interplay between antigen, HLA class II molecules and T cell receptors seem to be critical in the initiation of the sarcoid reaction (Baughman et al., 2011). Other non HLA polymorphisms suspected to play a role in the pathogenesis of sarcoidosis include genes encoding TNF-α (Kieszko et al,.2010), TGF-β1 (Jonth et al., 2007), BTNL2 (Rybicki et al., 2005), other proinflammatory cytokines, receptors (Fridlender et al., 2010; Schürmann et al., 2008) and other agents (Salobir et al., 2007). Results of these studies do not have universal value. Some results found in a defined ethnic group may not be confirmed in another. It may be concluded, however, that HLA-DRB1 and HLA-DQB1 alleles determine the susceptibility, phenotype and outcome in different populations (Rossman et al., 2003, Rybicki et al., 2003). From a vast armamentarium of different studied HLA class II polymorphisms, some evidently influence the course and outcome of sarcoidosis. The carriage of DR17 (DRB1*0301) in Swedish sarcoidosis patients is strongly linked to the development of Löfgren syndrome, rapid resolution of radiological changes and good overall prognosis, whereas patients with DR15 and DR16 genotypes are more likely to have chronic disease (Berlin et al., 1997). HLA DR17 patients were shown to accumulate T-lymphocytes in bronchoalveolar lavage fluid expressing the T-cell receptor V gene segment AV2S3 at disease onset (suggesting stimulation with a specific antigen), and the population of these cells normalized in recovered patients (Planck et al., 2003). The latter indirectly proves that this genotype may predispose to easier elimination of an unknown antigen from macrophages, which results in a rapid remission. The better prognosis in HLA-DRB1*0301 patients may be related to reduced Th1 response in the lung (Idali et al., 2006). In one of the latest studies, the same group of authors found that in a population of Swedes suffering from sarcoidosis, HLA alleles DRB1*01 and HLA DRB1*03 protected against non-resolving disease in non-Löfgren patients, and HLA DRB1*07, DRB1*14 and DRB1*15 were more frequently associated with chronic disease (Grunewald et al., 2010). The protective influence of HLA DRB1*01 was also shown in other populations of patients coming from United Kingdom, Poland, Czech Republic, and the Netherlands (Foley et al.., 2001; Sato et al., 2010a). Interestingly, HLA DRB1*0301 is absent among Japanese patients (Sato et al., 2010). A predominant occurrence of HLA DRB1*14 and its

linked DQ alleles in patients with insidious onset, chronic course, more advanced radiographic stage, and frequent relapses was also shown in Asian Indians (Sharma et al., 2003).

Interesting results are also delivered by studies on non-HLA polymorphisms. For instance, -765G>C promoter polymorphism in prostaglandin-endoperoxide synthase 2 gene, encoding a key regulatory enzyme in the synthesis of anifibrotic prostaglandin E2, may identify patients at increased risk of lung fibrosis (Hill et al., 2006). Other data suggest that the haplotype containing the -509C and codon 10T in the TGF-β1 gene predispose to more severe sarcoidosis, whereas -509T and codon 10C are protective (Jonth et al., 2007). CARD15/NOD 2 polymorphisms in the caspase recruitment domain and receptor for CC chemokine genes, which is common both in sarcoidosis and Crohn disease patients, may be responsible for severe courses of sarcoidosis (Sato et al. , 2010b). Other examples are increased risk of chronic or systemic sarcoidosis in patients with functional polymorphisms in COX-2 gene (Lopez-Campos et al., 2008), ACE gene (Tahir et al., 2007) or TNF-α gene (Kieszko et al., 2011; Sehan et al., 2008). The strong linkage was found between the -308G>A TNF-α (of positive prognostic value) and HLA DRB1*03 genes (Wijnen et al., 2010). Authors suggest that genotyping of one simple and less expensive TNF-alpha single nucleotide polymorphism can be used to predict the prognosis of pulmonary sarcoidosis in clinical practice. So far, genetic polymorphisms have not been used in clinical practice to predict the prognosis.

10. Clinical phenotypes

A variety of clinical and radiological presentations and different prognoses in patients suffering from sarcoidosis imposed the need of defining clinical phenotypes. It has been clear since the first description of acute sarcoidosis by Swedish pulmonologist Swen Löfgren that this complex of specific symptoms comprises a separate entity (Löfgren & Lundback, 1952). Patients with Löfgren syndrome are distinguished by an excellent prognosis. As described in the chapter on genetics, the susceptibility to acute sarcoidosis is determined by the carriage of a certain HLA DRB1 haplotype. In one study performed on a population of Swedish patients with acute onset of sarcoidosis, almost all patients positive for DRB1*0301/DQB1*0201 had resolving disease, whereas about half of DRB1*0301/DQB1*0201-negative patients presented with non-resolving sarcoidosis (Grunewald & Eklund, 2007). Therefore, even in so strictly defined phenotype the outcome within the group is also genetically determined.

At the other end of the spectrum of clinical presentations there is a non-resolving/progressive sarcoidosis, which is frequently accompanied by multiorgan involvement (systemic sarcoidosis). Genetic linkage analysis with clinical phenotypes revealed that genes influencing clinical presentation of sarcoidosis are likely to be different from those that underlie disease susceptibility (Rybicki et al., 2007).

Although there is no doubt that genetics play a crucial role in determining the chronicity, the type of exposure may also contribute to clinical presentation. For instance, agricultural organic dusts and wood burning was associated with significantly less likelihood of having extrapulmonary disease (Kreider et al., 2005). The "chronic" phenotype is much more poorly defined than an "acute," self-resolving phenotype. Besides, there is a variety of "intermediate" presentations in between which slip away from the definitions of these two main phenotypes. For scientific use, patients are frequently divided to "Löfgren" and "non-

Löfgren" subgroups, which reflects the obvious differences in prognosis. A novel protocol of phenotyping sarcoidosis was proposed based on these three criteria: 1. the type of onset (acute vs non-acute); 2. the need of treatment; 3. the need of long-term treatment (Prasse et al., 2008). According to these criteria, patients are further classified into 6 classes (table 1).

CLASS	DEFINITION
1	Acute onset, no need for immunosuppressive therapy
2	Acute onset, one period of treatment, not lasting longer than 1 year
3	Acute onset, need for several periods of immunosuppressive therapy or long-lasting treatment (>12 months)
4	Subacute onset, no need for immunosuppressive therapy
5	Subacute onset, one period of immunosuppressive treatment, not lasting longer than 1 year
6	Subacute onset, need for several periods of immunosuppressive treatment or long-lasting treatment (>12 mo)

Table 1. Protocol for clinical classification of sarcoidosis, proposd by Prasse et al . (2008).

The disadvantage of this classification is the need for long-term observation and lack of possibility to classify the patient to an appropriate category at the first visit. Table 2 shows clinical and laboratory features of "acute" and "chronic" phenotypes.

SELF-LIMITING DISEASE	CHRONIC DISEASE
Acute symptoms at onset	Subacute or subsidious onset
Radiological stage I and II	Radiological stage II, III, IV
Usually younger age at onset	Usually older age at onset
Acute phase reaction frequently present	Sporadic acute phase reaction
Frequent intensive lymphocytic alveolitis	Less frequent lymphocytic alveolitis, possible increased number of neutrophils and eosinophils in BAL
Systemic sarcoidosis unlikely	Systemic sarcoidosis likely
Rare altered calcium metabolism, especially rare hypercalcemia	More frequent altered calcium metabolism and nephrolithiasis

Table 2. Most important clinical features characterizing self-limiting and chronic phenotypes.

11. Conclusions

Several clinical and laboratory indices are used in everyday practice in order to estimate future prognosis in patients suffering from sarcoidosis. The most recognized are based on radiological classification and lung function test results. Patients with lung parenchymal involvement at presentation (radiological stage II and III) have worse prognosis comparing to patients with enlarged hilar/mediastinal lymhnodes only (stage I), although even in stage III spontaneous remissions are possible. The prognosis in patients with radiological signs of irreversible fibrosis (stage IV) is the worst, and these patients are at increased risk of respiratory insufficiency, death, and are potential candidates for lung transplantation. Impaired lung function at initial presentation or progressive impairment has obvious

negative prognostic value. Therefore, patients presenting with progressive lung infiltrates, especially when lung function impairment coexists, are candidates for long term treatment with steroids, other immunosuppressive drugs, or alternative therapy. Both restriction, best defined as decrease of TLC , and bronchial obstruction defined as decrease of FEV_1/FVC <70%, increase the risk of unfavorable outcome, i.e. risk of death, chronic course or need of chronic treatment. Decreased diffusion capacity for CO is a sensitive and useful marker of gas transfer impairment and may predict progression of sarcoidosis-related interstitial lung disease or indicate the need for screening towards pulmonary hypertension. The six-minute walk test is a simple exercise test which allows for selection of patients at increased risk of lung fibrosis and pulmonary hypertension. Different laboratory markers have been proposed, but none has been proven to be sensitive, specific and reliable enough to become a routine clinical test. Two laboratory markers are in clinical usage: serum angiotensin converting enzyme (SACE) and indices of calcium metabolic status (serum calcium concentration and 24 hrs urinary calcium loss). SACE has limited prognostic value, but altered calcium metabolism and nephrolithiasis may indicate the risk of chronic course. Increased number and percentage of lymphocytes in bronchoalveolar fluid (BALF) is not linked to worse prognosis, but increased content of neutrophils and eosinophils may have negative value.

There is a need for better defining sarcoidosis clinical phenotypes. It is clearly visible that patients with Löfgren syndrome constitute a different entity, not only in terms of different clinical course, but also in terms of evidently better prognosis. At the other end of this clinical spectrum are patients with chronic and progressive disease and involvement of multiple organs. There is no doubt, that these phenotypes are genetically determined, and especially some HLA DRB1 and DQB1 polymorphic alleles are responsible. Future studies will probably bring new genetic methods helpful in determining self-limiting and chronic phenotypes in everyday practice. They may be a promising new tool to select patients at highest need for therapy, and those who need more attention during clinical monitoring.

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13. References

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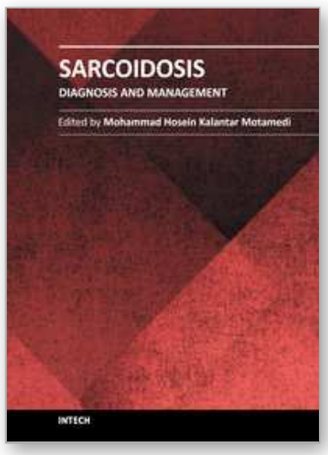
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Sarcoidosis Diagnosis and Management

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Sarcoidosis is a type of inflammation that occurs in various locations of the body for no known reason. Normally, when foreign substances or organisms enter the body, the immune system will fight back by activating an immune response. Inflammation is a normal part of this immune response, but it should subside once the foreign antigen is gone. In sarcoidosis, the inflammation persists, and some of the immune cells form abnormal clumps of tissue called granulomas. The disease can affect any organ in the body, but it is most likely to occur in the lungs. It can also affect the skin, eyes, liver, or lymph nodes. Although the cause of sarcoidosis is not known, research suggests that it may be due to an extreme immune response or extreme sensitivity to certain substances. It also seems to have a genetic component as well, and tends to run in families. Sarcoidosis most commonly develops in people between 20 and 50 years of age. African Americans are somewhat more likely to develop sarcoidosis than Caucasians, and females are somewhat more likely to develop sarcoidosis than males. The symptoms of sarcoidosis depend on the organ involved. This book deals with the diagnosis and treatment of this mysterious disease of unknown etiology.

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