Sarcoidosis is a multisystem disorder with variable prognosis – information for treating physicians

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Summary

Sarcoidosis is a chronic granulomatous inflammatory disorder of unknown origin with heterogeneous outcome. In most cases the disease is self-limited, others progress or die from organ involvement, which is often associated with extensive scarring. Although often the primarily affected sites are the lungs and thoracic lymph nodes patients with sarcoidosis must be staged for multiorgan involvement. Modern treatment strategies appraise a critical awareness for the side-effect-ratio of long-term medication. A main interest of research is to identify those patients with unfavourable outcome.

Key words: sarcoidosis; prognosis; gene expression; apoptosis; infliximab; tumour necrosis factor-alpha

Introduction

Sarcoidosis is a chronic multisystem disorder characterised by the presence of non-caseating granulomas and accumulation of T-lymphocytes and macrophages in multiple organs [1]. Up to date the most important enigma of sarcoidosis, ie its aetiology, remains unsolved. The other major challenge of sarcoidosis is its treatment. In some situations it is unclear whether a long-term immunosuppressive treatment should be started or whether one should just wait. Too many patients suffer from treatment-induced morbidity.

Epidemiology

The prevalence of sarcoidosis is estimated at 1–40 per 100 000 inhabitants [1–3]. It is seen throughout the world and affects all races, both sexes and all ages [1, 2]. There are geographical and racial differences in the occurrence of sarcoidosis [1, 4]. In the US sarcoidosis is 3–4 times more frequent in the black ethnicity [3–5]. In European countries sarcoidosis is more prevalent in northern compared to Mediterranean countries [2, 5]. The disease typically affects young adults between 10 to 40 years of age. Familial clustering and case aggregation have been reported [6, 7].

Aetiologic hypotheses

Various theories with arguments for infection, hypersensitivity and autoimmunity exist. In general it is thought that sarcoidosis may result from an exposure to an antigen (infectious agent, aerosols, etc.) in a genetically predisposed, susceptible host [4, 5].

The relationship between sarcoidosis and infectious pathogens is controversial and remains open to further investigation. Spatial, seasonal and occupational clustering is supporting the hypothesis of infective or other exogenous agents. Examples are the outbreaks on the Isle of Man, in northern Sweden or Hokkaido in Japan [6, 8, 9]. In Greece, Spain and Japan most cases are identified in spring and early summer. Certain professional groups appear to be at a higher risk. Clustering has
been noted in health care workers, fire fighters and naval aircraft servicemen in the USA [4]. Mycobacteria species, particularly cell wall-deficient forms, were proposed as aetiologic agents. Numerous studies have investigated this hot topic with diverse methodology and conclusions [10–13]. Evidence for a possible role for human herpesvirus 8, and propionibacteria has also been discussed [4, 14].

Genetics

There is a certain familial clustering (approximately 5–19% of cases) suggesting the importance of the genetic background [2]. First- and second-degree relatives of sarcoidosis cases have a significantly elevated risk of sarcoidosis compared with relatives of matched control subjects [15, 16]. Racial and ethnic background also has influence on prevalence and clinical presentation. Black subjects are more likely to have skin involvement other than erythema nodosum, as well as eye, liver, bone marrow and extrathoracic lymph node involvement [1, 16].

Sarcoidosis is a polygenetic disorder. Recent studies were able to demonstrate genetic risk factors (susceptibility genes) for the development of sarcoidosis and identified disease modifying genes associated with specific sarcoidosis phenotypes, like self-remitting stage I sarcoidosis or chronic progressive sarcoidosis. In a genome-wide analysis linkage to a section of the class II major histocompatibility complex (MHC) on the short arm of chromosome 6 was found [17]. Several alleles were associated with susceptibility (HLA DR 2, 11, 12, 14, 15, 17) or protective effects (HLA DR1, DR4 and possibly HLA DQ*0202) for sarcoidosis [4, 17, 18]. Rutherford et al. [18] found HLA-DR2 to be both a susceptibility and poor prognostic marker in sarcoidosis, and DR2-positive patients may particularly benefit from close follow-up and early treatment. In contrast, DR3-positive patients are at a lower risk of chronic disease. Future long-term studies on sarcoidosis probably require stratification for HLA-haplotypes.

Sarcoidosis has a broad spectrum of clinical presentations, which might be the consequence of different pathogenetic mechanisms, maybe even different diseases. Therefore, and to reduce the complexity of genotype/phenotype correlations different studies focussed on the Löfgren's syndrome, which represents a well-characterised homogenous phenotype. HLA DR*0301-DQB1*0201, CCR2 haplotype 2 and female sex were found to be associated with the development of Löfgren's syndrome in one study, but could not be confirmed by Schürmann et al. [19, 20]. Other data suggests that tumour necrosis factor-alpha, lymphotoxin-alpha and HLA-DRB1 gene polymorphisms or a gene located nearby contribute to the susceptibility to sarcoidosis and are associated (directly or via linkage with unknown causative locus) with Löfgren's syndrome [21]. Studies on polymorphisms of the angiotensin-converting enzyme (ACE) are inconclusive [22–25].

The significance and exact genetic locations still remain unclear. Further studies are needed to understand the molecular mechanisms that underlie these associations. The clinical usefulness of genetic tests in patients at risk or with manifest disease has not yet been shown.

Pathogenesis

The past few years have seen remarkable advances in understanding general immunologic and molecular aspects of the mechanisms leading to granuloma formation in sarcoidosis. Accumulation of macrophages and, particularly, CD4-positive T-lymphocytes are present at sites of disease activity, later conglomerating to form granulomata [26, 27]. The process seems to start with presentation of an unknown antigen to T-lymphocytes, via the MHC class II genes. Currently known mechanisms contributing to the cellular accumulation include (1) active migration of CD4-positive T-cells and monocytes from blood under the influence of potent chemotactic factors, including chemokines and respective receptors, MIP-1, MCP-1, RANTES and interleukin (IL)-2, IL-18 [28–35] and (2) in situ-proliferation of lymphocytes (IL-2 mediated, [36–39]) and possibly macrophages [40]. Chronic disease has been associated with TNF-alpha, IL-8 and ACE. On the other hand IL-10, IL-12, and IL-18 are said to play a role in disease resolution. However, the mechanism leading to the persistent accumulation of inflammatory cells is not fully understood. Whether or not reduced apoptosis is involved in the pathogenesis of sarcoidosis is unclear [41].
Clinical presentation

The clinical presentation of sarcoidosis is highly variable. The initial presentation is related to sex, race, and age [15, 16, 42, 43]. Thirty to sixty percent of patients remain asymptomatic, and the diagnosis is often an incidental finding [5]. Chronic dry cough, dyspnea and chest pain are the most common symptoms leading to medical attention. Nonspecific constitutional symptoms are frequent and include fatigue, malaise, fever, weight loss, muscle weakness, and exercise intolerance. The combination of fever, erythema nodosum, bilhar lymphadenopathy and polyarthralgias (Löfgren’s syndrome) is seen in 20–50% of cases [1, 2, 44–47]. Heerfordt’s syndrome (parotid swelling, uveitis, and Bell’s palsy) is another specific, but more rare sarcoidosis phenotype.

The pulmonary involvement can vary considerably and the initial radiological staging is a useful prognostic marker. The radiologic staging according to Siltzbach is based on conventional chest X-ray findings (see figure 1) [45]. Clinically relevant extrapulmonary involvement at initial presentation is seen in 7% of patients [1].

In nearly two-thirds of patients spontaneous remission occurs within 2–5 years, whereas chronic or progressive course of disease is observed in 10–30% of patients. Patients with erythema nodosum (eg Löfgren’s syndrome) are more likely to have a favourable course of disease [48]. Progressive sarcoidosis can lead to death in approximately 1–5% of cases, mainly due to progressive respiratory insufficiency, central nervous system or heart involvement [1].

Diagnostic criteria

Differential diagnoses

The diagnosis of sarcoidosis is made by exclusion because of a variety of other specific or unspecific granulomatous diseases. Careful history and clinical examination can be helpful in discriminating differential diagnoses from sarcoidosis. The main differential diagnoses include tuberculosis, fungal infections (eg histoplasmosis, coccidiomycosis), other specific infections (eg brucellosis, chlamydia, tularemia), autoimmune disorders (eg Wegener’s granulomatosis, Churg-Strauss vasculitis) and malignancies (eg lymphomas, carcinoma). Further important differential diagnoses include chronic beryllium disease, hypersensitivity to other metals/substances (titanium, aluminium, tcalc, etc.), exogenous-allergic alveolitis and drug-induced pneumonitis (eg methotrexate) [1, 2, 4, 43]. Multiorgan involvement increases the clinical likelihood of sarcoidosis [1]. Clinical presentation and histopathological details are equally important. Typical clinical features include bilateral lymphadenopathy, erythema nodosum, uveitis or other skin lesions (eg maculo-papular lesions, lupus pernio).

The need for biopsy

If sarcoidosis is suspected the diagnosis should be made with a biopsy whenever possible – except for rare cases of typical presentations of a Löfgren’s syndrome. The key pathological finding is the non-caseating granuloma. Due to the frequency of pulmonary involvement bronchoscopy is an important diagnostic tool. Bronchoscopy enables the investigator to identify endobronchial lesions, which can be found in almost half of the cases [2, 49, 50]. Simultaneously broncho-alveolar lavage (BAL) can be performed. The diagnostic yield of transbronchial lung biopsies (TBLB) varies from 40–90% and is depending on the stage of the disease and experience of the centre [1, 49, 51, 52]. Most researchers believe 4 to 6 specimens are needed, since sensitivity improves with the number of biopsies. Additional endobronchial biopsy (EBB), transbronchial needle aspiration (TBNA) or endobronchial ultrasound-guided lymph node biopsy (EUNA) can improve the diagnostic yield. Combining TBLB with EBB increases sensitivity by 10–21% [49, 51]. In one study EBB had higher overall diagnostic yield than TBLB [49]. EBB should be performed routinely, but certainly if mucosal abnormalities are present. Frequently patients with sarcoidosis have enlarged mediastinal and hilar lymph nodes. These are potential targets for TBNA or EUNA. With an 18-gauge needle a diagnostic yield of up to 90% can be achieved and add 10–20% to TBLB alone [51]. EUNA can further improve safety and diagnostic yield and will potentially reduce the need for mediastinoscopies in the near future.

In BAL a lymphocytic alveolitis with a CD4/CD8-ratio >3.5 is highly consistent with sarcoidosis. The sensitivity of CD4/CD8-ratio ranges from 42 to 59% and specificity from 76–96% [53–57]. Welker et al. report a positive predictive value of 69% in a group of patients with suspected interstitial lung disease [58]. BAL fluid lymphocyte counts do not predict disease progression or remission [51].

Imaging

Computed tomography of the chest can help to better characterise the pulmonary abnormalities, but is not a routine diagnostic tool [59–62]. HRCT can be helpful in discriminating inflammatory from fibrotic changes. It may detect parenchymal pathologies in patients with high sus-
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In patients with sarcoidosis HRCT has a yield of up to 92% of parenchymal findings [63]. Typical CT-findings are symmetric mediastinal and hilar lymphadenopathy, upper lobe predominance, peribroncho-vascular accentuation and subpleural micronodules (figure 1). Patients with predominantly ground-glass opacity and consolidation patterns on HRCT seem to have a worse prognosis than patients with predominantly nodular patterns and can develop honeycombing [64]. Magnetic resonance imaging (MRI) can help to diagnose brain, muscular-skeletal and heart involvement [4]. Nowadays, gallium scintigraphy is of limited value and should not be used routinely. Positron emission tomography (PET) is probably more sensitive and could help to identify ideal biopsy sites in special cases [65, 66].

Staging for extrapulmonary sarcoidosis

Sarcoidosis can affect virtually all organs. Therefore, all patients with this disease should be staged for extrapulmonary organ manifestation. Up to 90% of patients have lung involvement. In approximately 30% of patients extrapulmonary manifestations are found during the course of the disease. Organs frequently affected are peripheral lymph nodes, skin (approximately 25% of the cases), heart (5–10%), ocular involvement (25%), central nervous system (5%) and kidneys (rare).
Liver biopsies show granulomatous changes in 40–70% of the cases, but relevant hepatic dysfunction is rare [1, 2]. There are reports of an overlap with chronic inflammatory bowel diseases [16, 70, 71].

The clinical evaluation of patients with proven sarcoidosis should at least include thorough history (including occupational and environmental exposure), physical examination (emphasis on lung, skin, eye, liver, heart), chest radiography, pulmonary function tests (spirometry and diffusion capacity for carbon monoxide), blood count and chemistry (including calcium, liver enzymes, creatinine and urea), urine analysis (24h-calcium secretion), ophthalmologic examination and an electrocardiogram.

### Treatment

The unpredictable course of sarcoidosis – some patients showing spontaneous resolutions while others progress to chronic lung disease (ie fibrosis) – makes treatment decisions challenging. For many patients the most satisfying treatment is no treatment at all. The most important treatment options for sarcoidosis are summarised in table 1.

Corticosteroids remain the cornerstone of treatment. Oral and inhaled corticosteroids are widely used. In principle, only patients with severely active and/or progressive disease qualify for systemic treatment. However, there is no consensus about when and in whom therapy should be started or about dosage and duration. Some centres treat up to two thirds of their patients [72]. A recent Cochrane review [73] concludes that oral corticosteroids improved the chest radiograph, symptoms and spirometry over 3–24 months. But there is little evidence of an improvement in lung function or sustaining a long-term effect. Patients with stage II or III disease with moderate to severe symptoms and spirometry over 3–24 months. But there is little evidence of an improvement in lung function or sustaining a long-term effect. Patients with stage II or III disease with moderate to severe or progressive symptoms or changes on chest radiograph may have a benefit by oral corticosteroids. Patients with chronic active disease lasting longer than 2–5 years often need long-term therapy. The role for inhalative corticosteroids for patients with pulmonary sarcoidosis is not clearly established, and they do not seem to have a steroid-sparing effect. However, some trials show a benefit on clinical symptoms and lung function [1, 4].

Generally accepted indications and modalities for systemic immunosuppressive treatment are given in figure 2. If fatigue is incapacitating systemic therapy should also be considered. Dosage should be adapted according to clinical and symptomatic response. Usual dosage of steroids vary between 4–40 mg prednisone daily [73]. After an initial induction period, steroid dosage should then be reduced to the lowest possible maintenance level. Duration of therapy depends on indication and response.

Corticosteroid-sparing strategies with other immunosuppressive/immunomodulating agents are only partially successful, and sometimes associated with side effects (ie increased rate of infections). In case of skin lesions or involvement of anterior parts of the eye topical applications are the treatments of choice.

Due to the aetiologic coherence in granuloma formation and the association between high levels of TNF-alpha in BAL with chronic disease, a new strategy to interfere with the TNF-alpha pathway has been developed lately. Few recent reports have shown potential and in some cases respectable ben-

### Table 1

<table>
<thead>
<tr>
<th>Substance (Mechanisms)</th>
<th>Proposed use in sarcoidosis</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroids: Prednisone, Prednisolone (IL-2 &amp; TNF-α ↓)</td>
<td>Best studied drug; used for all forms of sarcoidosis; topical application ie skin, inhalation;</td>
<td>Osteoporosis, diabetes, hypertension, insomnia</td>
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<tr>
<td>Chloroquine, Hydroxychloroquine</td>
<td>Skin disease, neurosarcoidosis and hypercalcaemia; steroid-sparing in chronic pulmonary sarcoidosis</td>
<td>Ocular toxicity, nausea</td>
</tr>
<tr>
<td>Methotrexate (IL-2 release &amp; TNF-α ↓)</td>
<td>Acute and chronic sarcoidosis; effect delayed (6 months); steroid-sparing</td>
<td>Nausea, neutropenia, hepatotoxicity, pulmonary fibrosis</td>
</tr>
<tr>
<td>Azathioprine (IL-2 release &amp; TNF-α ↓)</td>
<td>Few data for chronic sarcoidosis; steroid-sparing</td>
<td>Nausea, neutropenia</td>
</tr>
<tr>
<td>Pentoxifylline (Lymphocytes &amp; TNF-α ↓)</td>
<td>Efficacy for acute (mild-moderate) disease</td>
<td>Gastrointestinal intolerance (common)</td>
</tr>
<tr>
<td>Thalidomide (IL-12 release &amp; TNF-α ↓)</td>
<td>Useful for chronic skin disease; no effect on pulmonary disease, anti-angiogenic</td>
<td>Somnolence, teratogenic, constipation, peripheral neuropathy</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>Because of toxicity only for refractory cases</td>
<td>Neutropenia, nausea, cystitis, carcinogenic</td>
</tr>
<tr>
<td>Cyclosporine (IL-2 release &amp; T-cell activation ↓)</td>
<td>Possible effect for neurosarcoidosis; no clinical improvement; no steroid-sparing effect</td>
<td>Renal failure, hypertension, can cause lymphoma</td>
</tr>
<tr>
<td>TNF-alpha antagonists: Infliximab (monoclonal antibody against TNF-alpha) (Etanercept)</td>
<td>Limited data about effectiveness and dosage; possible use for refractory disease</td>
<td>Increased rate of tuberculosis, allergic reaction, possibly carcinogenic</td>
</tr>
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Sarcoidosis research

Despite intensive research the aetiology and the markers of unfavourable clinical course in sarcoidosis remain challenging issues. Large epidemiological trials helped to improve staging and risk assessment for patients. Among other findings the ACCESS study revealed that women were more likely to have eye and neurologic involvement and erythema nodosum, whereas men were more likely to be hypercalcaemic [15, 16]. In the future new diagnostic markers like CD103/CD4 ratios in BAL might improve non-invasive diagnosis [80].

Studies on the pathogenesis of granuloma formation investigated different inflammatory response pathways. A region of interest is the c-c chemokine receptors. An association between specific CCR5 haplotype (HHC) and persistent lung involvement in sarcoidosis was reported [81]. T-lymphocytes co-expressing CXCR3 and CXCR6 seem to act coordinately with respective ligands and Th1-type inflammatory cytokines in the alveolitic/granuloma phases of the disease [82].

Genome-wide linkage analyses underline the importance of the MHC region to confer a genetic risk for sarcoidosis [17, 83]. Currently, an association with susceptibility to sarcoidosis is investigated for the BTNL2 gene, which resides in the class II MHC region of chromosome 6p and is probably involved in co-stimulation of T-lymphocytes [17, 83, 84]. Many groups are currently searching to understand the exact molecular mechanisms and genetic locations that underlie these associations.

In order to find prognostic markers and potential therapeutic targets new technologies are applied. Gene expression arrays are able to measure many thousands of genes at once. A recent study [41] found that mechanisms controlling apoptosis are playing a key role in the pathogenesis of sarcoidosis. Significant differences in the expression of apoptosis-related genes were found in peripheral blood of patients with acute onset sarcoidosis [18, 41, 85]. Using a target gene approach strategy...
early growth response-1 (EGR-1), an immediate early gene, was found to be associated with chronic fibroproliferative lung involvement. EGR-1 was found over-expressed in lung biopsies of sarcoidosis patients. When blocking EGR-1 in an in vitro model of primary human lung fibroblasts, the proliferation of these cells was significantly abrogated [86].

The patients’ perspectives

Sarcoidosis often hits young adolescent patients, who just finished their professional education, and are about to found a family. They find themselves in a situation, where it is unclear whether they suffer from a progressively invalidating or a “flu-like” disease. This relevant uncertainty – potentially triggered by other mechanisms – leads to a relevant proportion of patients with depression [87, 88]. An open-minded discussion about the impact of the disease on the daily life and mood is very important, and not rarely a psychotherapy with or without the application of an antidepressant medication is indicated.

Another concern of patients with sarcoidosis is that their family physicians or even lung specialist often have little experience with this rare disease and misinterpret their symptoms, which delays diagnosis in many cases. It would often be easier for them to directly see a specialist for sarcoidosis [89]. Patients often seek for alternative treatment approaches with varying response. So far there is no respective evidence.

Future directions

As long as the aetiology of sarcoidosis is unclear, there are no effective prevention strategies. Better and more gene-based prognostic criteria are needed in order to identify individuals, who require closer follow-up and/or immunosuppressive treatment. Novel pharmacological agents that are more specific than corticosteroids to block inflammation, granuloma formation, and organ scarring, are urgently needed.

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