Chapter 1

General introduction

Sarcoidosis

Sarcoidosis has been known for more than 100 years; it was first described by the dermatologist Hutchinson, and several years later by two other dermatologists, Besnier and Boeck.

Sarcoidosis is a multi-organ inflammatory disorder that is characterized by a specific morphological hallmark, noncaseating granuloma (figure 1.1).[1-4] Although the exact etiology remains unknown, current evidence supports the concept that the pathogenesis of sarcoidosis involves a highly polarized T-helper 1 (Th1) immune response to pathogenic tissue antigens or specific environmental factors.[1] Granuloma formation is regulated by a complex interaction between T-helper lymphocytes and macrophages, in which cytokines such as tumour necrosis factor (TNF)-α play an important role (figure 1.2).[4-7]

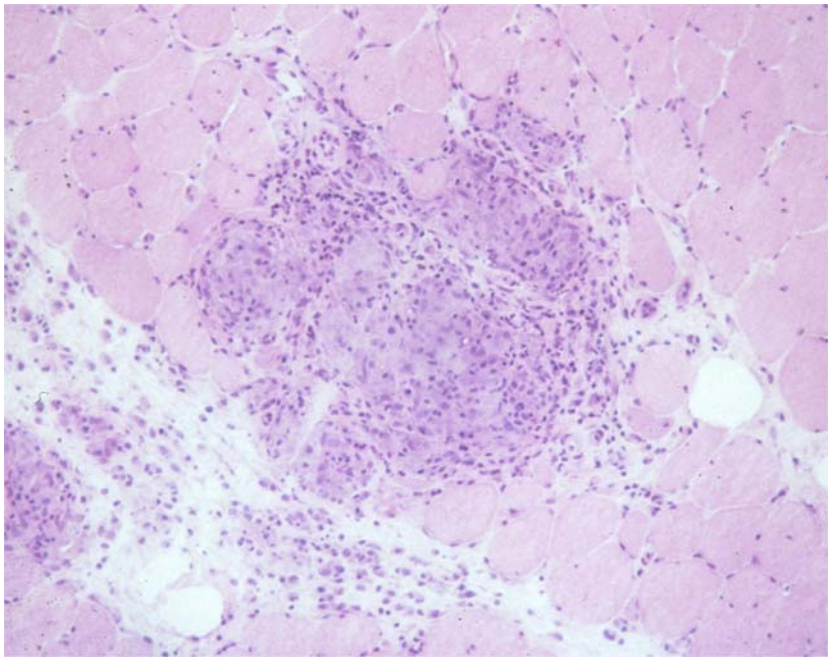

Figure 1.1. Noncaseating granuloma present in a biopsy obtained from the left quadriceps muscle of a sarcoidosis patient (100X).

Conventional treatment is focused on attenuating granuloma formation with antimalarial drugs that inhibit antigen presentation or with nonspecific anti-inflammatory agents such as glucocorticosteroids, methotrexate, or azathioprine.[4] Anti-TNF-α agents such as infliximab and thalidomide have recently shown some success in sarcoidosis.[4,8-15] Designing future therapies depends on improved knowledge of the critical immunological processes operative in different stages of disease.[16]

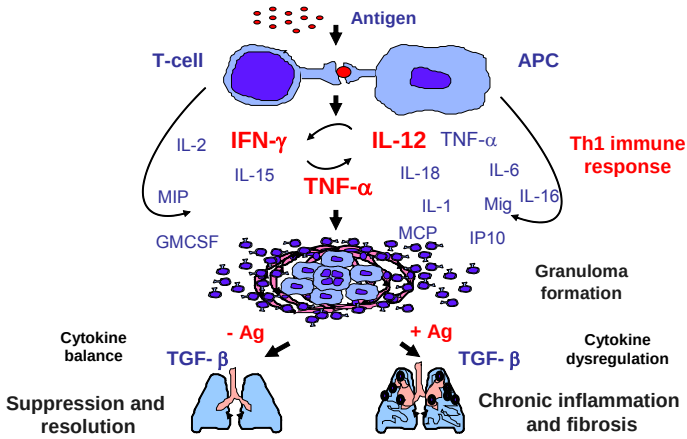

Figure 1.2. Hypothetical model of the pathogenesis of sarcoidosis. An inciting agent induces antigen-specific, Th1-mediated granulomatous inflammation with production of Th1 cytokines such as interferon (IFN)-γ and interleukin (IL)-2. Macrophages, activated directly by the inciting agent and by IFNγ, produce IL-12, TNF-α, IL-6 and other cytokines important in cell activation, proliferation and recruitment. Activated macrophages and T-cells along with other effector cells such as fibroblasts, orchestrate the complex process of granuloma formation under the regulatory influence of local cytokine production. Removal of inciting agent allows immunosuppressive cytokines such as tumour growth factor (TGF)-β to downregulate the immune response with return to cytokine homeostasis. Granuloma regression likely occurs by cell apoptosis. Persistent antigenic stimulation results in cytokine dysregulation and possibly, T-cell autoimmune responses. If untreated, chronic antigenic stimulation and cytokine production results in tissue injury which, together with upregulated production of TGF-β and other profibrotic cytokines, lead to irreversible fibrosis (adapted with permission from Moller).[6]

Clinical features of sarcoidosis

The clinical course of sarcoidosis is highly variable and depends on ethnicity, duration of illness, site and extent of organ involvement, and activity of the granulomatous process, which shows a tendency to wax and wane. Mode of presentation varies from asymptomatic, to an “acute onset” presenting as Löfgren`s syndrome with erythema nodosum, fever, arthralgia and enlarged lymph nodes at the chest radiograph and finally to a chronic course, frequently accompanied with non-specific constitutional symptoms such as fatigue, pain, and general muscle weakness. The true number of asymptomatic patients cannot be reliably determined since in many of them the diagnosis is not established. Practically every organ can be involved. However, most cases (>90%) have respiratory symptoms such as cough and dyspnoea and/or abnormal chest radiographs. Furthermore, the lymphoid system, skin, eyes, heart, nervous system, and liver may be involved.[1,4,17]

Prognosis of acute onset sarcoidosis is good and spontaneous remission usually occurs within two years while chronic sarcoidosis mostly has an insidious onset. The course of chronic sarcoidosis is often relapsing with resolution being less likely. In some of the cases the disease is progressive. Development of lung fibrosis, cardiac sarcoidosis and neurosarcoidosis are related to worse prognosis. Up to 5% will eventually die from sarcoidosis.[2] A rare however dramatic complication in sarcoidosis is sudden death.

As mentioned above, many sarcoidosis patients suffer from apparently non-specific symptoms such as pain and fatigue.[18-21] However, these symptoms do not often reflect disease activity. They have been so far an enigma to physicians treating sarcoidosis patients and are a major problem that has a great impact on the quality of life of sarcoidosis patients.[21-24] The following cases illustrate some of these symptoms:

Case 1

A 55-year old male known with pulmonary sarcoidosis since two years was referred to the neurology department because of severe pain in hands and lower legs and feet with paraesthesias. He could not stand bed-clothes on his legs, and wore short trousers without socks in winter because he could not stand clothes on his lower legs. Furthermore, he was suffering from severe fatigue, profuse sweating, diarrhoea, bladder emptying difficulties, sicca syndrome, paroxysmal palpitations with dizziness after which he collapsed once, and erectile dysfunction. Neurological examination revealed no abnormalities except subjective dysesthesia of the lower legs and feet. Differential diagnosis included neuropathy with involvement of autonomic fibers. Electromyography, nerve conduction studies and cardiovascular autonomic function tests were normal. Temperature threshold testing (TTT) revealed abnormal temperature sensation

compatible with small fiber neuropathy (SFN). He was treated with prednisone without any success, and subsequently put on methotrexate, again without any improvement. Neuropathic pain treatment[25-28] with gabapentin, amitryptilin, carbamazepin, local capcaicin cream were all without benefit. Opioids gave some pain reduction and improved diarrhoea. However, after a few weeks he developed urine retention. At present the patient is severely disabled mainly because of severe pain and fatigue and had to stop working.

Case 2

A 39 year-old male known with pulmonary and neurological involvement (hydrocephalus) of sarcoidosis since 2000 presented at the neurology department for a second opinion in 2003 with symptoms of extreme fatigue, cognitive impairment, pain in palms and soles, weakness of the legs and finally dizziness and blurred vision while standing. He had been suffering from these symptoms since 2 years. Former elsewhere performed cerebral MRI revealed unchanged hydrocephalus without any parenchymal lesions and lumbar puncture had showed normal pressure and normal cell counts, protein, and glucose levels. The posture dependent symptoms in combination with pain in palms and soles were suspective of SFN. Therefore, TTT was performed revealing severely abnormal temperature sensation. Cardiovascular autonomic function testing showed a normal blood pressure response after changing position from supine to standing but an abnormal increase in heart rate (63 beats/minute; normally less than 30 beats/minute). Furthermore, blood pressure modulation frequency in the upright position was too low (0.051 Hz). Both results as well as the symptoms are consistent with the diagnosis of postural tachycardia syndrome (POTS). He was treated with hydration, increased salt intake and elastic support hose without much benefit. At present he is on fludrocortisone 50 ug daily with which he feels a bit better.

We observed that a similar pattern of symptoms occurred frequently in sarcoidosis patients consisting of peripheral pain, fatigue and vegetative symptoms such as diarrhoea, micturation disturbances, erectile dysfunction, sicca syndrome, sweating, heat intolerance, flushes, orthostatic pain in the coat-hanger area and recurrent collapses while under the shower. We assumed that this reoccurring pattern of symptoms was suggestive of the presence of SFN as a common complication in sarcoidosis. This hypothesis was the basis of this thesis.

Small fiber neuropathy

SFN is a neuropathy selectively involving small diameter myelinated and unmyelinated nerve fibers. Interest in this disorder has considerably increased during the past few years. Routine electrodiagnostic studies, which primarily test large myelinated fiber function, are mostly normal in these patients. The syndrome of SFN has been an enigma to practitioners because of the unexplained contrast between severe pain in the extremities and a paucity of findings in neurological and electrophysiological examination. Recent advantages in diagnostic techniques (TTT, cardiovascular autonomic function testing, and intra-epidermal nerve fiber density (IENFD) assessment in skin biopsy) facilitate objective confirmation of clinical diagnosis and the characterization of fiber type involvement in SFN. Diagnosis is made on the basis of the clinical features, normal nerve conduction studies, and abnormal specialized tests of small nerve fibers.

Scope and aims of the study

The aims of the present study were to explore the presence and different aspects of neurological involvement, pain and in particular SFN in sarcoidosis.

In ***chapter 2*** the existing literature regarding neurosarcoidosis is reviewed to give an overview of the present knowledge and dilemmas clinicians are faced with diagnosing and treating patients with neurosarcoidosis. An approach for the diagnosis of neurosarcoidosis, as well as treatment strategies, are discussed.
Chapter 3 reviews the literature regarding what is known about SFN. Furthermore, pathophysiology hypotheses and present treatment are described here. Finally, suggested areas of further research regarding SFN are discussed.
The aim of ***chapter 4*** was to explore the presence and impact of pain in sarcoidosis. This was performed in a Dutch sarcoidosis population (n=821) using questionnaires.
The aim of ***chapter 5*** was to analyse the presence of sleep problems, restless legs and periodic leg movements in sarcoidosis.
In ***chapter 6*** we describe the assessment of SFN in sarcoidosis using various types of testing: temperature threshold testing, sympathetic skin response and cardiovascular autonomic function testing.
The aim of ***chapter 7*** was to further objectify the presence of SFN in sarcoidosis using skin biopsy.
The aim of ***chapter 8*** was to develop and validate a list to screen for the presence of SFN. Besides for screening this list can be valuable in future longitudinal and therapeutic studies.

The aim of ***chapter 9*** was to investigate whether SFN in sarcoidosis might be associated with cardiac autonomic dysfunction. Therefore, we performed iodine-123 meta-iodobenzylguanidine (^{123}I-MIBG) scintigraphy, cardiovascular autonomic function testing and temperature threshold testing, besides several tests for cardiac evaluation to assess whether there is a relation between SFN with cardiac sympathetic dysfunction in sarcoidosis.

The aim of ***chapter 10*** was to analyse the role of genetic factors in sarcoidosis related SFN. For this purpose the association between human leucocyte antigen (HLA), SFN and disease course in sarcoidosis was explored.

In ***chapter 11*** the improvement of SFN in a refractory sarcoidosis patient after treatment with anti-TNF-α therapy (infliximab) is described.

In ***chapter 12*** a summary and implications of the findings presented in this thesis are argued and directions for future research are briefly discussed.

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