REVIEW

Sarcoidosis: The Disorder, Its Diagnosis, and Its Treatment

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Abstract

Sarcoidosis is a widespread immunity disorder, which can present itself in numerous different ways, but most primarily as a pulmonary disorder. In this literature review, the current state of scientific knowledge on the symptoms, pathophysiology, diagnostics, and treatment of the disorder is laid out. A brief historical introduction to sarcoidosis is also provided. It is found that sarcoidosis has a highly variable set of symptoms, which include patches on the skin and pulmonary dysfunction. The main mechanics of this disorder seem to surround T-cell and macrophage hyperactivity, resulting in the formation of granulomas and, if expressed in the lungs, pulmonary fibrosis. Diagnostic methods include biopsy, imaging, and biomarker analysis. Currently, treatment rests mostly on corticosteroids, though other medications can be of use, depending on the type of manifestation. The prognosis of the disorder is found to be varied: In most cases it will disappear spontaneously, but overall the mortality ranges from 1 to 10% of all cases. Definite, specific medication is not within reach yet, though with further research this might change.

Introduction

Sarcoidosis is a disorder that commonly affects young adults (aged 20-40) and presents itself most often in the lungs and on the skin [1]. The disorder causes the formation of granulomas: inflamed areas which, in the case of sarcoidosis, are of unknown etiology. These granulomas can show up in any organ [2]. A study by Baughman et al. [3] suggests that 95.0% of all sarcoidosis patients show granulomas in the lungs and 15.9% on the skin. It also suggests that, next to age, race and sex may affect both the moment of presentation and the characteristics of the presented sarcoidosis. A great geographical variation is observable, as the prevalence in the United Kingdom is far lower (approximately 19 cases per 1,000,000) than for example the United States of America (approximately 33 cases per 100,000) [1,4].

The disorder itself was first formally described by the English pathologist Sir Jonathan Hutchinson in 1877 as a skin disorder [5]. 140 years later, the amount of knowledge on the disorder is still relatively low: the cause is unknown and diagnosis can be difficult due to the "diverse, nonspecific or initially misleading presentations" [6]. While genetic factors are suspected to play a role, as for example monozygotic twins have a higher rate of disorder than dizygotic twins, this idea has not been substantiated yet [1, 2]. The symptoms, pathophysiology, diagnostic procedures, treatment, and prognosis of this interesting disorder will be discussed in order to create a structured overview.

Symptoms

As the disorder can manifest itself in virtually any organ, the range of symptoms found for sarcoidosis is quite extensive. The organs that are involved may vary over time, meaning that the symptoms will change accordingly.

Pulmonary sarcoidosis The most prevalent presentation of sarcoidosis, the pulmonary manifestation, shows symptoms that can easily be misdiagnosed as a different pulmonary disorder. Examples of these symptoms are: dyspnea, cough, chest discomfort, and crackles [7]. These symptoms provide little-to-no insight on the disorder or its severity. However, as sarcoidosis can be asymptomatic as well, it is common to discover sarcoidosis in a routine chest X-ray. Such an X-ray image can show four different stages of the disorder, as shown in figure 1: stage I will show only bilateral hilar lymphadenopathy (BHL); stage II will show BHL in combination with pulmonary infiltrates; stage III will show pulmonary infiltrates, without BHL; stage

IV will show fibrosis [1]. BHL is the enlargement of the lymph nodes of pulmonary hila, which usually comes without any symptoms. Asymptomatic, however, does not mean that the disorder can be ignored. It will walk up the ladder of stages as described before, increasing the severity of the disorder. It is also possible for other organs to become involved in the disorder at a later point in time.

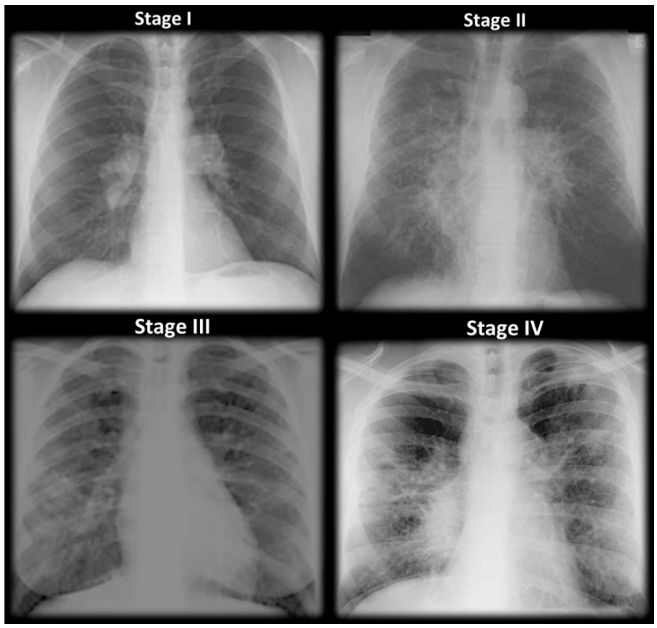

Figure 1: The four different stages of pulmonary sarcoidosis - From: Jara-Palomares et al. [8] *Staging of sarcoidosis on basis of chest radiographs*. Clinical Manifestations of Sarcoidosis. In: Eishi Y, editor. Sarcoidosis. This work is licensed under a Creative Commons Attribution 3.0 Unported License. © The Authors.

Other types and symptoms of sarcoidosis. Outside of the lungs, a wide range of symptoms can be presented as well, such as plaques or nodules on the skin, inflammation of the eye, as well as vascular change in the retina [6]. These symptoms can be expressed in different intensities in different ethnical groups. African American men, for example, are "more likely to have skin involvement," according to Baughman et al. [3]. The same study suggested that women have a higher chance of a manifestation in the eyes, as well as an increased chance of neurological involvement, which, once again, portrays the extensive range of possible symptoms.

Pathophysiology

The primary abnormalities in sarcoidosis consist of granulomas and, in the case of pulmonary sarcoidosis, pulmonary fibrosis. Even though the actual cause of sarcoidosis is still unknown, the mechanisms of the aforementioned abnormalities are quite well understood.

Granulomas. Sarcoidosis is the exaggeration of an immune response to a particular antigen, which could originate from the immune system recognizing specific "pathogen-associated" patterns in the molecular structure of mycobacteria and propionibacteria, after they have been (partially) killed, as described in a seminar by Valeyre et al. [6]. The list of other possible antigens is, however, not limited to these waste products. Other compounds, both organic and inorganic, might also be triggers for sarcoidosis [6]. These compounds can be inhaled at any moment in a person's life and, in the case of microbial waste, are sometimes non-degradable. The compounds and waste materials trigger specific immunity receptors, as these receptors will recognize the patterns as antigens. This will stimulate a T-cell response, which consequently stimulates a macrophage response. In a healthy person, this interaction will be suppressed by alveolar macrophages, but in a person diagnosed with sarcoidosis the alveolar macrophages have above-average antigen-presenting capabilities. These capabilities, caused by an upregulated expression of MHC-2 molecules and co-stimulators, will result in the exaggerated immune response [6]. The actual formation of the granulomas is caused by this response, as the overstimulated macrophages will "differentiate into epithelioid cells, gain secretory and bactericidal capability, lose some phagocytic capacity, and fuse to form multinucleated giant cells" [7].

Pulmonary fibrosis. Even though these granulomas are able to resolve spontaneously and with relatively small consequences, the risk of developing pulmonary fibrosis does not resolve. Up to 20% of all sarcoidosis patients will develop this type of fibrosis [9]. The pathophysiology of this development is still partially speculated, in contrast to the mechanism behind granulomas. Certain proteases have been observed in increased quantities in bronchoalveolar-lavage specimens from patients with sarcoidosis, while an increase in the inhibitor of this protease was not present [7]. This means that proteases are able to break the extracellular matrix down without any inhibiting factors. Another factor that might play a role is the reaction of macrophages to the increased activity of T-cells.

These macrophages will produce high amounts of fibronectin and CCL18, which enhance collagen production by the fibroblasts in the lungs. These upregulated fibroblasts enhance the production of CCL18 in macrophages, thus creating a positive feedback loop, which can lead to pulmonary fibrosis [7].

Diagnostics

The three primary diagnostic measures that can be taken in order to diagnose sarcoidosis are chest imaging, a biopsy, and exclusion of other granulomatous disorders [2]. Next to these three measures, the serum biochemistry can be studied, lung function tests can be conducted, as well as a full blood count [1]. A new method for the diagnosis of BHL, as described by Valeyre et al. [6], is endobronchial ultrasound-guided transbronchial needle aspiration.

Primary measures. *Chest imaging.* An X-ray image can be used in order to assess the involvement of the lungs. However, it is unreliable to use it as a definitive diagnosis of sarcoidosis, as extrapulmonary sarcoidosis is a possible manifestation too; therefore, the severity of sarcoidosis must be assessed by different measures. High-resolution CT is a more viable option for this task, as it is more accurate and can portray a better overview [2]. *Biopsy.* The next step in the case of a positive identification of sarcoidosis is to confirm the diagnosis by means of either biopsy or exclusion of other disorders. In the case of biopsy, a tissue sample will be examined in order to confirm the presence of granulomas. These samples can be taken from skin lesions (if present), lymph nodes, lung tissue, as well as other possibly affected regions [2]. *Exclusion of other granulomatous disorders.* When symptoms and X-ray signs are minimal, the possibility that another disorder is stimulating granuloma-formation must be ruled out. Tissue samples will have to be cultured, and occupational and environmental factors have to be assessed, in order to confirm the diagnosis of sarcoidosis in the differential diagnosis [2].

Secondary measures. When the primary measures are not sufficient for a valid diagnosis, secondary measures can provide further information on the type and/or severity of the disorder. The serum biochemistry in a patient with suspected sarcoidosis can contain high amounts of calcium (hypercalciuria), due to metabolic disturbances in the sarcoid macrophages. Hypercalciuria is observed in only 40% of sarcoidosis patients, therefore it is not a primary assessment [7]. In patients with suspected pulmonary sarcoidosis, lung function can be tested in order to confirm the diagnosis. Kumar & Clark [1] note that a decrease in total lung capacity (TLC) can be observed, which could be due to the pulmonary infiltrates and fibrosis caused by sarcoidosis. FEV¬1 and FVC can also be decreased because of the decreased elasticity of the lungs. Because of the alveolar granulomas, the gas transfer is decreased as well. Next to the testing of lung function, a full blood count can be done as well. If the patient has sarcoidosis, normochromic, normocytic anaemia can be observed, in combination with an elevated erythrocyte sedimentation rate, indicating an inflammation [1, 7].

Treatment

When the manifestation of sarcoidosis is mild or asymptomatic, the patient does not need any form of treatment, next to being monitored for further deterioration. The disorder will often resolve by itself. If this is not the case after 6 months of monitoring, it is advised to start treatment with prednisolone [1, 2]. Immediate treatment is recommended if the risk of death, major organ dysfunction, or incapacitation is at a sufficient level [6]. When the patient is diagnosed with pulmonary sarcoidosis, treatment with corticosteroids is advised, as these patients are less likely to spontaneously improve. In the case of a stage IV manifestation of pulmonary sarcoidosis, a consistently efficient treatment for the pulmonary fibrosis is not available on the market. In eye involvement, or when calcium levels in the blood are persistently elevated, treatment with systemic steroids is mandatory [1, 2]. Next to these corticosteroids, cytotoxic drugs can be prescribed, as well as cytokine modulators and antimicrobial drugs. The specific type of medication is based on the type of manifestation of sarcoidosis, as its origin and symptoms are of such diversity [6]. Most of the aforementioned medications target a specific protein (TNF-alpha), which normally plays a role in systemic inflammation. In sarcoidosis, this protein causes the granulomatous response and keeps this response in motion [6].

Prognosis

Prognosis for sarcoidosis is varied, not only as a result of the severity and origin of the disorder, but

also as the result of racial differences. In general, the mortality ranges from 1 to 5% [10], but, as mentioned, this range differs between ethnic groups. The mortality rate in African Americans is recorded to be up to 10% of all cases [1]. This mortality rate has been shown to be 12 times higher than that of Caucasians in the United States of America, resulting in a mortality rate of just below 1% [11]. In the United Kingdom, the overall mortality rate is estimated to be less than 5% [1]. The cause of death is often respiratory failure and pulmonary heart disease. In some cases, damage to the renal system, or a myocardial manifestation of sarcoidosis is the cause of death, but these are uncommon [1]. Two-thirds of all patients with stage I pulmonary sarcoidosis recover within a timeframe of two years, the same is true for half of all stage II patients and one third of all stage III patients [1]. Serial monitoring is obligatory, as the disorder can recur. This recurrence can happen within two years of the remission of the disorder, and has been observed in less than 10% of patients with a spontaneous remission. Up to 30% of all patients contract a chronic form of sarcoidosis, these are the patients in which the disorder does not remit within two years [2].

Conclusion

The symptoms, pathophysiology, diagnostics, treatment and prognosis of sarcoidosis have been described in a concise manner, in order to create an overview of the disorder and its pathological influence on the human body. Sarcoidosis is a disorder with highly variable symptoms, a mechanism of which parts are still speculation, non-specific diagnostic procedures, non-specific drugs – or even no treatment at all, and a variable prognosis. The progress of research on sarcoidosis is slow, because it is such a dynamic disease with a quite complex pathological mechanism; therefore, it could take years before a specific cure, or even a specific diagnostic procedure for this disorder is developed.

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