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Sarcoidosis

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Introduction

Sarcoidosis was first identified over one hundred years ago by two dermatologists, Dr. Jonathan Hutchinson in England and Dr. Caesar Boeck in Norway. It is a **multi-organ, inflammatory disease** characterized by the formation of granulomas. The cause of the disease is unknown. Sarcoidosis can appear suddenly and disappear spontaneously. In some cases, it can develop gradually with symptoms that can last a lifetime, leading to the eventual formation of fibrosis in the affected tissues. Sarcoidosis is the most common of the fibrotic lung disorders.

Definition

Sarcoidosis is a disease of unknown etiology characterized by widespread granulomatous lesions that may affect any organ or tissue of the body. Although it can appear in most organs, it most often begins in the **lungs** or lymph nodes. The name for the disease originated from the Greek words "sark" and "oid", meaning flesh-like. It was originally called Hutchinson's Disease or Boeck's Disease.

Classification

Sarcoidosis is classified as a granulomatous disorder that is likely a result of an immunological response to an antigenic trigger. Sarcoidosis is viewed as a condition in which both host and environmental factors contribute to the phenotype.

Consequences

In 60-70% of affected individuals, the sarcoidosis spontaneously regresses within two years of onset with or without treatment National Heart, Lung, and Blood Institute (1995). It has been estimated that 20-30% of sarcoidosis patients develop permanent lung disease (fibrosis). Chronic sarcoidosis occurs in 10-15% of patients that develop sarcoidosis. Sarcoidosis is fatal in 5-10% of patients who have granuloma formation in vital organs, such as the **lungs**, **heart**, **liver**, or **central nervous system**.

Associated Disorders

Sarcoidosis may be associated with **multi-organ inflammation**. Eventual granuloma formation and fibrosis may develop.

Etiology

A specific etiologic agent has not yet been identified for sarcoidosis. It is believed that sarcoidosis results from a complex interaction of multiple genes with environmental exposures or infection Thomas and Hunninghake (2003). Evidence suggests that sarcoid granulomas are formed in response to a persistent, poorly degradable antigenic stimulus. Investigations aimed at identifying specific agents, such as **viruses**, mycobacteria, and environmental organic and inorganic antigens, have not definitely demonstrated an association with sarcoidosis.

Epidemiology

Sarcoidosis occurs throughout the world, being found in almost all races and in both sexes. However, it is most prevalent in African-Americans and northern European whites, and it is mainly a disease of young adults. The age of onset is usually between 20-40 years of age, although it can appear in children and the elderly. It is estimated that 5 in 100,000 white people and 40 in 100,000 African-Americans have sarcoidosis in the United States National Heart, Lung, and Blood Institute (1995). Sarcoidosis has long been recognized as a common disease in Scandinavian countries, where it is estimated to affect 64 out of 100,000 people.

Pathophysiology

It is believed that an unknown stimulus activates quiescent T-lymphocytes and macrophages and leads to the release of pro-inflammatory cytokines and chemokines at the sites of the disease Du Bois et al (2003), Ziegenhagen and Muller-Quernheim (2003). Most commonly, this occurs in the **lungs** and lymph nodes. The cytokines cause recruitment, activation, and proliferation of mononuclear cells, generate inflammation, and promote granuloma formation. Experimental studies have demonstrated that sarcoidosis is characterized by enhanced expression of the immunomodulatory cytokines, interferon-gamma (IFN-gamma) and interleukin-12 (IL-12). These cytokines promote **cellular immunity** and stimulate amplification of the immune response by enhancing the expression of tumor necrosis factor-alpha (TNF-alpha) and other effector cytokines and chemokines involved in inflammatory cell trafficking. Due to its role in granuloma formation, TNF-alpha is believed to be an important mediator of inflammation and cellular immune responses associated with sarcoidosis. TNF-alpha increases fibroblast proliferation and collagen synthesis. Data suggest that genetic polymorphisms lead to inter-individual differences in cytokine production. It is then possible that cytokine genotypes might influence the predisposition and severity of sarcoidosis.

Signs and Symptoms

Approximately 30-60% of reported sarcoidosis cases are asymptomatic Thomas and Hunninghake (2003). For others, the most common symptoms include respiratory complaints (e.g., dry cough, dyspnea, chest pain), skin rashes (e.g., erythema nodosum, papules, nodules), systemic effects (e.g., fever, night sweats, fatigue, malaise), ocular problems (e.g., eye pain, visual changes), and musculoskeletal ailments (e.g., joint pain, myalgia).

Standard Therapies

In the majority of sarcoidosis patients, no treatment is necessary because the symptoms are usually not disabling and the disease tends to disappear spontaneously. In the statement issued by the American Thoracic Society/European Respiratory Society/World Association of Sarcoidosis and other Granulomatous Disorders regarding treatment of sarcoidosis, several specific conditions were identified that require therapy Hunninghake et al (1999). These include cardiac or neurological involvement, hypercalcemia, and ocular diseases that cannot be controlled by topical therapy. Treatment is not always required for pulmonary involvement. In most cases, symptomatic pulmonary disease and patients with worsening lung function are treated. Most of the treatments for sarcoidosis are anti-inflammatory agents that directly suppress the development and maintenance of granuloma formation by influencing cytokine and chemokine release and immune cell interactions Moller (2003). Oral corticosteroids are the drugs of choice for the treatment of this condition. When steroid therapy fails, the second line of treatment includes immunosuppressive/cytotoxic agents, such as **methotrexate**, **cyclophosphamide**, **azathioprine**, or **antimalarial drugs**, such as **hydroxychloroquine** and **chloroquine**.

Agent Name	*Discussion*
Glucocorticoids: Prednisone and Prednisolone	Glucocorticoids (**prednisone**, **prednisolone**) have broad-spectrum, anti-inflammatory effects on multiple cells including T-lymphocytes, macrophages, and granulocytes Moller (2003). They inhibit the expression of many pro-inflammatory cytokines, such as IL-1, **IL-2**, IL-4, IL-5, IL-6, **IL-8**, IL-12, IFN-gamma, and TNF-alpha. Despite their widespread use in the treatment of sarcoidosis, there is little evidence of long-term benefit Baughman et al (2003). In addition, chronic treatment with corticosteroids is associated with serious side effects, including **diabetes**, **hypertension**, **osteoporosis**, **insomnia**, and immunosuppression.
Immunosuppressive/cytotoxic agents: Methotrexate, Cyclophosphamide, Azathioprine	Clinical data suggest that the effectiveness of immunosuppressive/cytotoxic agents (**methotrexate**, **cyclophosphamide**, **azathioprine**) in the treatment of sarcoidosis is highly variable. Their use should be restricted to those requiring long-term treatment or who have central nervous system, cardiac, or other progressive conditions refractory to glucocorticoid therapy Thomas and Hunninghake (2003). Side effects associated with these drugs include nausea and neutropenia.
Antimalarial agents: Hydroxycloroquine and Chloroquine	The effectiveness of **antimalarial agents**, such as **hydroxycloroquine** and **chloroquine**, in the treatment of sarcoidosis is quite variable. These drugs are useful steroid-sparing agents for the treatment of chronic pulmonary sarcoidosis requiring high-dose glucocorticoid therapy Baughman et al (2003). They are used for skin and mucosal sarcoidosis if treatment is indicated and corticosteroids are not needed Moller (2003). Side effects to antimalarial agents include nausea and ocular toxicity.

Experimental Therapies

Various agents that suppress TNF-alpha either directly or indirectly have been tested as treatments for sarcoidosis. Clinical studies suggest that antiTNF-alpha therapy may help in some cases of sarcodisosis Baughman et al (2003). However, the choice of drug and the type of patient to treat has yet to be established with this drug class.

Combination therapy using different combinations of drugs is becoming more popular for the treatment of sarcoidosis Baughman and Lynch (2003). A cocktail or combination of drugs with different mechanisms of actions has been used for the treatment of chronic or refractory sarcoidosis in an attempt to reduce side effects and improve efficacy.

Agent Name	*Discussion*
Tumor necrosis factor-alpha inhibitors: Infliximab, Etanercept, Pentoxifylline, Thalidomide	Several tumor necrosis factor-alpha inhibitors have been examined as experimental therapy of sarcoidosis. Infliximab is a murine monoclonal antibody targeted against TNF-alpha and has been shown to be useful in refractory sarcoidosis Baughman et al (2003), although it has been noted to increase the risk of tuberculosis infection. **Etanercept** blocks the TNF-alpha receptor and was not as likely to be associated with tuberculosis. **Pentoxifylline** is a phosphodiesterase inhibitor shown to block the release of TNF-alpha by alveolar macrophages Baughman et al (2003). Nausea is the most common side effect associated with pentoxifylline treatment. **Thalidomide** blocks TNF-alpha release from alveolar macrophages and suppresses granulomatous responses. Side effects for thalidomide include sedation, constipation, peripheral neuropathy, and teratogenesis, which is a major concern.

Other Information – Web Sites

American Lung Association: www.lungusa.org/diseases/lungsarcoido.html This is a freely accessible website maintained by the American Lung Association that provides a brief but informative background on all aspects of sarcoidosis.

National Sarcoidosis Resource Center: www.nsrc-global.net This is a free website that provides a comprehensive information and communication resource for sarcoidosis.

Sarcoidosis Online Sites: www.sarcoidosisonlinesites.com The purpose of this free website is to offer a comprehensive list of websites to educate those afflicted with sarcoidosis to help in the search for better treatment, and to aid in finding a cure for the disease.

National Heart, Lung, and Blood Institute: http://www.nhlbi.nih.gov/health/public/lung/other/sarcoidosis/sarcoid.pdf This is a National Institutes of Health document which gives a complete overview of sarcoidosis and is a good source of information for patients and the public.

Medline Plus Medical Encyclopedia: http://www.nlm.nih.gov/medlineplus/ency/article/000076.htm#Treatment

This is a U. S. National Library and a National Institutes of Health sponsored website that provides an overview of sarcoidosis in an encyclopedia-type format.

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Further Reading

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