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- Sarcoidosis is an illness that generates tremendous anxiety among persons who suffer from it and interest among the individuals who provide care to them. The disease occurs throughout the world and has been around for more than 150 years. Its colorful history, which has been documented before, is provided in this article.
- Etiology of Sarcoidosis** 365
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- Research over the past decade has advanced our understanding of the pathogenesis of sarcoidosis and provided new insights into potential causes of this disease. It is important to remember that any etiologic agent of sarcoidosis must be capable of causing the pathologic hallmark of systemic noncaseating granulomas and the heterogeneous clinical features of sarcoidosis. In addition, etiologic agents must be compatible with immunologic features, including polarized T-helper 1 cytokine profiles and oligoclonal T cell expansions consistent with antigen driven processes. Yet, even with studies conducted in this disease, there remains a lack of consensus on the etiology of sarcoidosis. This challenge is likely to be overcome only with additional research that incorporates clinical, genetic, immunologic, environmental, and microbiologic profiles in groups of patients, supplemented with testing of candidate pathogenic agents in experimental models that recapitulate critical features of this disease.
- The Immunology of Sarcoidosis** 379
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- Sarcoidosis continues to be a disease of research interest because of its complicated immune mechanisms and elusive etiology. So far, it has been established that granulomatous inflammation in sarcoidosis is predominately a T-helper 1 immune response mediated by a complex network of lymphocytes, macrophages, and cytokines. The cause of progression to a chronic and potentially fibrotic form is unclear but may involve loss of apoptotic mechanisms, loss of regulatory response, or a persistent antigen that cannot be cleared. Recent genomic and proteomic technology has emphasized the importance of host susceptibility and gene–environment interaction in the expression of the disease.

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Sarcoidosis is a multigenic and multifactorial disease. Predisposing genes have been identified and fast progress in molecular technologies including systematic genome-wide association studies and large-scale resequencing will aid the discovery of further risk loci and variants. The exploration of the molecular epidemiology of genetic variants in the pathogenesis of sarcoidosis will allow an assessment of their prognostic usefulness. To this end, different granulomatous disorders of known and unknown etiology should be investigated jointly by genetic, immunobiological, and proteomic approaches. The definition of individual genetic risk profiles in sarcoidosis and other chronic inflammatory disorders seems achievable and a useful route for clinical translation.

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The diagnosis of sarcoidosis can never be assured: sarcoidosis is a diagnosis of exclusion and this cannot be accomplished with complete confidence. The diagnosis requires clinicoradiographic findings compatible with the diagnosis, histologic confirmation of granulomatous inflammation, exclusion of known causes of granulomatous disease, and evidence of disease in at least two organs. The end result of this diagnostic evaluation for sarcoidosis is neither a definitive diagnosis nor an exclusion of the diagnosis, but rather a statistical likelihood of the disease.

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Sarcoidosis is a disease with protean clinical manifestations ranging from no symptoms to sudden death. Radiologic tests are often the key to diagnosis. In this article, the authors review current imaging techniques and discuss emerging technologies used in the noninvasive cardiopulmonary evaluation of the patient who has sarcoidosis.

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Sarcoidosis is characterized by intense inflammation at the different sites of localization. Many different mediators, such as cytokines, chemokines, and other proteins with various functions, that participate in its complex pathogenesis have been proposed as markers of inflammation. This article examines the principal literature on these different markers analyzed in serum, bronchoalveolar lavage, expired breath, and urine. After many years of research, no single marker sufficiently sensitive and specific for diagnosis of sarcoidosis has yet been found. Greater correlation with clinical parameters is needed and proper validation.

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Sarcoidosis is an inflammatory granulomatous disease that is characterized by diverse organ system manifestations, a variable clinical course, and a predilection for affecting relatively young adults worldwide. Abnormalities on chest radiographs are detected in

85% to 95% of patients who have sarcoidosis. Approximately 20% to 50% of patients who have sarcoidosis present with respiratory symptoms, including dyspnea, cough, chest pain, and tightness of the chest. The clinical course and manifestations of pulmonary sarcoidosis are protean: spontaneous remission occurs in approximately two thirds of patients; up to 30% of patients have chronic course of the lung disease, resulting in progressive, (sometimes life-threatening) loss of lung function. Morbidity that correlates to sarcoidosis occurs in 1% to 4% of patients.

Neurosarcoidosis

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Elyse E. Lower and Kenneth L. Weiss

Although neurosarcoidosis seems to occur in only 5% to 10% of patients who have sarcoidosis, it may lead to significant complications. The diagnosis of neurosarcoidosis usually relies on indirect information from imaging and spinal fluid examination. Although MR imaging remains the most sensitive technique for detecting neurologic disease, other tests, including positron emission tomography scanning and cerebral spinal fluid examination, can provide important information. The role of immunosuppressive agents such as methotrexate, cyclophosphamide, and azathioprine has been expanded, and these agents should be considered for the treatment of some manifestations of neurosarcoidosis. Reports of the antitumor necrosis factor agent infliximab suggest that this drug can be helpful for patients who have neurosarcoidosis.

Cardiac Sarcoidosis

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Uma S. Ayyala, Ajith P. Nair, and Maria L. Padilla

Sarcoidosis is a systemic disease with a favorable prognosis, high remission rate, and low mortality. Cardiac involvement alters this prognosis. Clinical manifestations most commonly include arrhythmias, conduction abnormalities, and congestive heart failure. Treatment includes immunosuppressant therapy, permanent pacemakers in the setting of conduction abnormalities, and implantable cardioverter-defibrillators in patients at risk for sudden cardiac death. Risk stratification for sudden cardiac death is essential in otherwise asymptomatic patients who have suspected cardiac sarcoidosis.

Hepatic, Ocular, and Cutaneous Sarcoidosis

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Anthony S. Rose, Marcus A. Tielker, and Kenneth S. Knox

Sarcoid affecting the skin, eye, or liver can be symptomatic of or cause significant morbidity. When disease is severe, alternative therapies may be needed.

Quality of Life and Health Status in Sarcoidosis: A Review of the Literature

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Jolanda De Vries and Marjolein Drent

The quality of life and health status are impaired in patients suffering from sarcoidosis, especially in those who have clinical symptoms. Fatigue is an integral part of the clinical picture of sarcoidosis, but is an underestimated problem in clinical practice. Objective test results do not always correlate with the well-being of the patient. Present studies are generally cross-sectional. There is a need for prospective follow-up studies assessing the natural course of patients' disease in relation to symptoms and quality of life.

Treatment of Sarcoidosis

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Robert P. Baughman, Ulrich Costabel, and Ronald M. du Bois

Not all patients who have sarcoidosis require treatment. For those who require treatment, the outcome of sarcoidosis can be considered conceptually in three broad, and

at least partially overlapping, groupings: acute, chronic, and refractory. Although corticosteroids remain the initial drug for most patients who require therapy, several steroid-sparing alternatives have been found effective in treating many aspects of sarcoidosis. Methotrexate is most commonly used cytotoxic agent used for chronic disease, but azathioprine and leflunomide also have been shown to be useful. The tumor necrosis factor antibody infliximab has proved useful in treating refractory sarcoidosis. These various agents led to a treatment strategy for the various aspects of sarcoidosis.

Pulmonary Hypertension Caused by Sarcoidosis

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Enrique Diaz-Guzman, Carol Farver, Joseph Parambil, and Daniel A. Culver

Pulmonary hypertension is an uncommon complication of sarcoidosis, but in severe pulmonary disease it occurs frequently. It is an important cause of cryptogenic dyspnea in sarcoidosis patients and can occur despite the absence of pulmonary fibrosis. The true prevalence is unknown. With the advent of specific therapies for pulmonary hypertension, there has been a resurgence of interest in the pathophysiology, diagnosis, and treatment of sarcoidosis-associated pulmonary hypertension. This article reviews the status of the current epidemiologic, pathophysiologic, and therapeutic knowledge regarding this entity.

Outcome of Sarcoidosis

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Sonoko Nagai, Tomohiro Handa, Yutaka Ito, Kousuke Ohta, Manabu Tamaya, and Takateru Izumi

Sarcoidosis is a chronic granulomatous inflammatory disease of unknown etiology with heterogeneous outcome. Based on the natural history or clinical treatment course, the outcomes of cases can be divided into two wings: spontaneous regression (self-limited disease) or progression of extensive fibrotic lesions as a postgranulomatous fibrosis. In addition to examining these outcomes, this article focuses on several related concepts, including chronicity (persistence of the lesions), relapse/recurrence, deterioration, and mortality. It also reviews the outcomes from the point of view of relevant clinical phenotypes, the natural disease course, the effects of treatment, and the effects of lung transplantation. Finally, it considers the effects of pulmonary hypertension, various genetic factors on the outcomes, and the efficacy of several novel therapeutic drugs in treating sarcoidosis.

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