Top Ten List in Sarcoidosis*

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Abbreviations: ACCESS = A Case Control Etiologic Study of Sarcoidosis; CCR2 = chemokine C receptor 2; CCR2–64I = chemokine C receptor 2 gene polymorphism V64I; FNAB = fine-needle aspiration biopsy

Etiology


The increase in our knowledge of the immune mechanisms leading to the formation of the sarcoid granuloma unfortunately has not resolved the key question dealing with the etiologic agent(s) causing the disease. In this article, many genomes of Propionibacterium acnes or Propionibacterium granulosum were detected in specimens from 15 lymph node biopsies from 15 patients with sarcoidosis by using a quantitative polymerase chain reaction assay.

The data suggest an etiologic link between propionibacteria and some cases of sarcoidosis. In particular, it is proposed that sarcoidosis may arise from a Th1 immune response to one or more antigens of propionibacteria in an individual with a hereditary or acquired abnormality of the immune system. Indeed, even if it is known that P acnes is a strong adjuvant, causing granulomas when injected experimentally into sensitized rats and rabbits, further experimental data are needed to draw definite conclusions about the pathogenetic role of propionibacteria in sarcoidosis.

Pathogenesis


Alveolar immunocompetent cells produce a number of chemokines during the different phases of the hypersensitivity reaction which characterizes sarcoidosis, including CXC chemokines and CC chemokines. The expression of chemokine receptors is genetically determined. For instance, a transition causing a valine-to-isoleucine substitution in transmembrane domain I of the chemokine C receptor 2 (CCR2) gene polymorphism V64I (CCR2–64I) has a protective effect against the progression of HIV-1 infection. With this information as a background, this report examines the clinical features of sarcoidosis in relation to the polymorphism of the CCR2 gene, coding for the main receptor for the monocyte chemotactic protein group of CC chemokines.

It has been shown that the distribution of the CCR2–64I allele significantly differed between subjects with sarcoidosis and healthy control subjects. In addition, the presence of the CCR2–64I allele conferred a lower risk for the development of sarcoidosis. These intriguing data suggest the hypothesis that genetic differences in the amount or quality of chemokine receptors could have consequences for the trafficking of immune cells and, thus, for the variations in the clinical phenotypic expression of inflammatory events that take place at sites of disease activity in patients with sarcoidosis.

Guidelines


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This fundamental article is the result of three meetings of a Joint Commission formed by experts of the American Thoracic Society, the European Respiratory Society, and the World Association of Sarcoidosis and Other Granulomatous Disorders. All known aspects of sarcoidosis are considered, and a number of useful guidelines for the diagnosis of, management of, and therapy for the disease are provided.


This is an organ assessment system for sarcoidosis developed by the Steering Committee of a Case Control Etiologic Study of Sarcoidosis (ACCESS), which includes investigators at the 10 ACCESS Clinical Centers, the Clinical Coordinating Center, and representatives of the National Heart, Lung, and Blood Institute. The aim of the ACCESS system is to provide an instrument that helps clinicians to clarify and define a probable organ involvement in patients with known sarcoidosis.

It is advised that the proposed instrument is partially subjective in that it depends on the clinician’s diligence in pursuing evidence for sarcoidosis involvement in various organs. Nonetheless, it is hoped that a correct application of this instrument might lead to an increased standardization in the definition of organ involvement in patients with sarcoidosis.

**DIAGNOSIS**


Baughman RP, Iannuzzi MC. Diagnosis of sarcoidosis: when is a peek good enough [editorial]? Chest 2000; 117:1004–1011

In a study of 28 patients, the utility and relative cost-effectiveness of fine-needle aspiration biopsy (FNAB) in the clinical settings of patients with sarcoidosis is analyzed. Anatomic sites of the 32 FNABs include lymph node, lung, salivary gland, and liver. All aspirates showed granulomatous inflammation. FNAB was more cost-effective than tissue biopsy.

It is suggested that FNAB, if used in conjunction with radiologic and laboratory data, is a reliable method of diagnosis that may replace the more costly surgical biopsy. As remarked in the editorial com-

**THERAPY**


An approach to the use of steroids for pulmonary sarcoidosis is proposed. Steroid treatment is split into the following six phases: (1) initial high doses to control inflammation; (2) tapering to a maintenance dose that will continue to suppress the inflammation but will lessen the risk of corticosteroid toxic reactions; (3) continuing with a maintenance dose of corticosteroids until a decision to taper off is made; (4) tapering off corticosteroid therapy; (5) observing for relapse; and (6) treatment if relapse occurs. The article considers the approach for the use of corticosteroids in terms of the above six phases and provides recommendations for the daily dose adjustment and time period in which steroids should be used.


At present, methotrexate is the only alternative immunosuppressive drug that has been studied in great detail for therapy in patients with sarcoidosis who do not respond to corticosteroids or show steroid side effects. This is a randomized study aimed at determining whether methotrexate can be used as a steroid-sparing agent in patients with acute sarcoidosis. Twenty-four patients with new-onset, biopsy-proven symptomatic disease within 4 weeks of starting prednisone therapy were randomized to receive either methotrexate or placebo for the following year. The patients were seen monthly, and the prednisone dosage was tapered following a predetermined schedule. Less prednisone was used in patients randomized to the maintenance group, suggesting that methotrexate is an effective steroid-sparing agent for the first year of steroid therapy in patients with acute sarcoidosis.


Chloroquine has been proposed as an alternative drug for long-term treatment of sarcoidosis but has...
not been accepted as standard therapy. This randomized trial assesses the efficacy of prolonged chloroquine therapy in 23 symptomatic patients with biopsy-proven chronic pulmonary sarcoidosis. Patients had been treated for 6 months with chloroquine, 750 mg/d, tapering every 2 months to a dosage of 250 mg/d. The initial treatment led to a significant improvement in symptoms, pulmonary function, angiotensin-converting enzyme level, and the results of a lung gallium scan. Patients randomized to the maintenance group (chloroquine, 250 mg/d) showed a slower decline in pulmonary function and had fewer relapses than did the observation group (no chloroquine). Side effects have been observed only with high doses of chloroquine. This promising study suggests that chloroquine may be effective in controlling chronic pulmonary sarcoidosis.

ASSOCIATION


This is a large retrospective cohort study that evaluates the relationship between systemic sarcoidosis and malignant neoplasms, a topic that has been widely debated in the last few years. The clinical data of 474 consecutively diagnosed cases of sarcoidosis at Uppsala University Hospital, Sweden, from 1966 to 1980 and 8,541 patients identified in the Swedish Inpatient Register from 1964 to 1994 were linked to the Swedish Cancer Register, the Register of Causes of Death, and the Register of Total Population. Patients with sarcoidosis appear to be at a significantly increased risk for cancer, in particular lung cancer, malignant lymphomas, and cancer in organs known to be involved in sarcoidosis (including cancer of the eye, nasal sinuses, and buccal cavity). The study suggests that chronic inflammation may be a putative mediator of the increased risk in sites affected by sarcoidosis.

LUNG TRANSPLANTATION


This study examines the long-term benefit of lung transplantation in nine patients with end-stage lung disease secondary to sarcoidosis who underwent single-lung transplantation. All transplant recipients survived beyond postoperative day 30, with five recipients still alive. The 1-year survival rate for this group was 67% (six of nine patients).

As shown by sequential lung biopsy procedures, five of the patients had recurrences of granulomata in their lung allografts without radiographic evidence or clinical symptoms related to granulomatous inflammation. There was no significant difference in the prevalences of high-grade acute cellular rejection (histologic grades III and IV) and of chronic rejection (obliterative bronchiolitis) between recipients who had sarcoidosis and other recipients all of whom underwent single-lung transplantation for COPD or other inflammatory lung diseases. It is concluded that lung transplantation is a valid alternative for end-stage lung disease secondary to sarcoidosis.