Tumor Necrosis Factor Polymorphism in Sarcoidosis

Sarcoidosis is an antigen-driven, multisystem, granulomatous disorder, the cause of which is not known. In a genetically susceptible individual, antigen-presenting cells trap, process, and present the putative antigen, in the context of class II major histocompatibility complex (MHC) molecules, to CD4+ lymphocytes. The result of this union is a coordinated release of cytokines and chemokines, which recruit more inflammatory cells (lymphocytes, mononuclear phagocytes, and fibroblasts) and mount a granulomatous response dominated by interferon-γ and interleukin-12,1,2

If the antigen(s) are removed or destroyed, the granulomatous response subsides; however, persistence of the antigenic stimuli results in lasting disease. In a small number of patients, profibrotic cytokines, including transforming growth factor-β and tumor necrosis factor (TNF)-α, appear and move the inflammatory process towards fibrosis.

There is little doubt that genetic factors play an important role in the genesis of sarcoidosis.3 During the later half of the last century, many reports of familial sarcoidosis appeared. In a study4 of 16 families drawn from two international sarcoidosis clinics, the disease showed a preponderance of monozygous over dizygous twins, like-sex over unlike-sex pairs, and mother-child over father-child association. Rybicki et al5 showed that African Americans have a threefold increased risk of familial sarcoidosis as compared with control subjects. McGrath et al6 conducted a questionnaire survey to identify the risk ratio for siblings of familial sarcoidosis. Twenty-four of the original 406 index patients (5.91%) were found to have at least one other relative with biopsy-proven sarcoidosis, supporting the hypothesis that a shared determinant, either genetic or environmental, was involved in familial sarcoidosis.

Newly developed molecular genotyping techniques are now being applied to explore genetic aspects of the disease. The TNF family consists of at least 15 cytokines that play an important role in inflammation and immune response. The three important members of this family are TNF-α (also called TNF), TNF-β (also called lymphotoxin-α), and lymphotoxin-β. The genes for these three related cytokines lie at the telometric end of the class III region of the central MHC. Activated monocytes/macrophages and T-cell subsets are the major sources of TNF. It is synthesized as a proprotein comprising 233 amino acids with a molecular mass of 26 kDa. The proprotein is processed by a specific metalloprotease called TNF-α-converting enzyme to a monomeric, active 17 kDa soluble form comprising 157 nonglycosylated amino acids. The expression of TNF-β (lymphotoxin-α) is restricted in being produced by T and B cells as a soluble molecule.7-10 Despite it being structurally related to TNF, the biologic function of TNF-β is not clearly appreciated. Because of the human leukocyte antigen (HLA) localization of the TNF-α and β genes, many investigators have focused on the role of TNF polymorphism in HLA-associated diseases, particularly insulin-dependent diabetes mellitus, ankylosing spondylitis, other autoimmune disorders, and cerebral malaria.11-14 In a large case-control study in Gambian children, McGuire et al13 found that, homozygous for TNF2 allele, a variant of TNF-α gene promoter region had higher circulatory levels of TNF-α and a higher risk for death or complications due to cerebral malaria. Although the TNF2 allele was in linkage disequilibrium, the authors13 showed that complications of malaria were independent of HLA class I and class II variation. Thus, regulatory polymorphism of the cytokine gene affected the outcome of malarial infection. In sarcoidosis, increased production of TNF-α has been found.15,16 Seitzer et al17 studied TNF-α and TNF-β polymorphism in 101 patients with pulmonary sarcoidosis and 216 healthy blood donors. A higher frequency of the more uncommon TNF-α2 allele was found in patients with Lofgren syndrome, a benign form of acute, spontaneously remitting sarcoidosis.17 Since TNF-α2 is associated with higher level of TNF-α production, it is reasonable to assume that higher TNF-α production, may be instrumental in influencing the granulomatous process. Takashige et al18 found a significant increase in TNF-α2 allele with high TNF-α production in Japanese patients with cardiac sarcoidosis who had prolonged illness, an entirely different observation.

In this issue of CHEST (see page 753), Dr. Yamaguchi and colleagues provide evidence supporting the role of TNF polymorphism in sarcoidosis. Three biallelic polymorphisms in the promotor region of TNF-α gene were genotyped by direct sequencing of polymerase chain reaction (PCR). Three genotypes of the TNF-β intron 1 polymorphism (TNF-β*1/1, homozygous for TNF-β*1; TNF-β*1/2, heterozygous for TNF-β*1 and TNF-β*2/TNF-β*2, homozygous for TNF-β*2) were detected by Nco1 restriction length polymorphism analysis of PCR products spanning intron 1 and exon 2 of the TNF-β gene. They found no evidence of TNF gene polymorphism conferring susceptibility to sarcoidosis or any relationship between TNF-β polymorphism and clinical manifestations of the illness.19 Nonetheless, the patients with the allele TNF-β*1
had chronic course. Since TNF-β*1 is associated with higher TNF-α production, it is tempting to speculate that increased TNF-α production may predispose patients to prolonged illness. Their study, however, was limited to Japanese patients with a relatively benign course not requiring corticosteroid therapy. Although Yamaguchi and colleagues provide evidence that TNF genotypes predispose individuals to developing sarcoidosis, they justifiably contend that TNF polymorphism may influence the course of sarcoidosis in a selected group of Japanese patients.

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Endoluminal Metastases of the Tracheobronchial Tree
Is There Any Way Out?

Metastatic spread to the lungs from other than bronchopulmonary tumors is a common clinical problem. The incidence of lung metastases is estimated to from 20 to 50% in nonpulmonary primary tumors. This is thought to be because of the role of the lungs as the primary capillary filter of the drainage of most organs. Tumors more likely to give lung metastases are breast, renal, GI, thyroid, germ cell, carcinomas, as well as sarcomas and malignant melanomas.1,2

A major clinical problem in patients with nonpulmonary primary tumors is the endoluminal metastasis to the tracheobronchial tree. The incidence of such a metastasis is estimated to be approximately 2%.3,4 However, it seems that endoluminal metastases are underestimated. A study5 reported a higher incidence (28%) of endobronchial metastases in patients with metastatic disease. The main cause of this discrepancy is that fiberoptic bronchoscopy is not performed systematically in all patients with pulmonary metastasis.6 Patients with endoluminal metastasis may also have parenchymal lesions, and the diagnosis is provided by means other than bronchoscopic procedures, such as transthoracic biopsy or fine-needle aspiration or even open-lung biopsy.7 In addition, these patients may have low performance status as well as poor prognosis; physicians, aware of their patients’ quality of end of life, deny performing invasive techniques.8 Thus, there is an evident selection bias in the estimation of the incidence of endoluminal metastasis to the tracheobronchial tree.

The differential diagnosis of endotracheal/endobronchial metastasis and primary lung cancer may be difficult.5,9 Presenting symptoms, such as cough, hemoptysis and dyspnea, as well as chest radiograph