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The clinical and immunologic features of pulmonary fibrosis in sarcoidosis

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Sarcoidosis is a multisystem, granulomatous disease that most often affects the lungs. The clinical course is highly variable; many patients undergo spontaneous remission, but up to a third of patients progresses to a chronic disease course. The development of pulmonary fibrosis (PF) in a subset of patients with chronic disease has a negative impact on morbidity and mortality. While sarcoidosis-associated PF can be progressive, it is often referred to as "burnt out" disease, a designation reflecting inactive granulomatous inflammation. The immune mechanisms of sarcoidosis-associated PF are not well understood. It is not clear if fibrotic processes are active from the onset of sarcoidosis in predisposed individuals, or whether a profibrotic state develops as a response to ongoing inflammation. Transforming growth factor β (TGF-β) is an important profibrotic cytokine, and in sarcoidosis, distinct genotypes of TGF-β have been identified in those with PF. The overall cytokine profile in sarcoidosis-associated PF has not been well characterized, although a transition from a T helper 1 to a T helper 2 signature has been proposed. Macrophages have important regulatory interactions with fibroblasts, and the role of alveolar macrophages in sarcoidosis-associated PF is a compelling target for further study. Elucidating the natural history of sarcoidosis-associated PF will inform our understanding of the fundamental derangements, and will enhance prognostication and the development of therapeutic strategies. (Translational Research 2012;160:321–331)

Abbreviations: ANXA11 = annexin A11; Arg1 = arginase 1; BTNL2 = butyrophilin-like protein 2; BMPs = bone morphogenic proteins; CIP = chronic interstitial pneumonitis; CXR = chest x-ray; GM-CSF = granulocyte-macrophage colony-stimulating factor; GREM1 = gremlin 1; HRCT = high resolution computed tomography; IFN-γ = interferon gamma; IPF = idiopathic pulmonary fibrosis; M1 = classically activated macrophage; M2 macrophage = alternatively activated macrophage; MCP-1 = monocyte chemotactic protein-1; MIP-1b = macrophage-inflammatory protein-1b; PF = pulmonary fibrosis; PGE2 = prostaglandin E2; RANTES = regulated on

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Conflict of interests: None.

Submitted for publication November 18, 2011; revision submitted March 14, 2012; accepted for publication March 16, 2012.

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1931-5244/$ - see front matter

doi:10.1016/j.trsl.2012.03.005

activation, normal T cell expressed and secreted; TGF-β = transforming growth factor-β; Th1 = T helper 1; Th2 = T helper 2; Tregs = T regulatory cells; TNF-α = tumor necrosis factor-α

Sarcoidosis is a complex, granulomatous disease of unknown etiology. Many organ systems can be affected, although lung involvement is most common, occurring in greater than 75% of all patients. The clinical outcomes in sarcoidosis are highly variable. While more than half of patients undergo remission with no significant residual morbidity, a subset of patients develops chronic disease. By convention, chronic sarcoidosis is disease activity lasting at least 2 years.[1] Chronic sarcoidosis is itself a heterogenous category, which subsumes a variety of types of organ damage, including pulmonary fibrosis (PF). Immunosuppression is variably effective in controlling disease activity. There is no cure for sarcoidosis, although lung transplantation can be life saving for those with severe lung involvement.[2]

Pulmonary fibrosis occurs in up to 20% of patients with sarcoidosis and is of important consequence: it is associated with increased morbidity, a higher risk of pulmonary hypertension, the need for lung transplantation, and increased mortality.[3-8] We herein summarize the evaluation of sarcoidosis-associated PF, and review the immunopathologic underpinnings as they are currently understood. We highlight the recognized differences between nonfibrotic and fibrotic pulmonary sarcoidosis, and between idiopathic pulmonary fibrosis (IPF) and sarcoidosis-associated PF. Microscopic fibrosis, representing a normal healing response to inflammation, may be evident on sarcoid histology. When small and stable foci of fibrosis do not result in significant radiographic changes or functional impairment, they likely do not affect the clinical course of sarcoidosis. For the purpose of this review, sarcoidosis-associated PF refers to an extensive fibrotic process which results in clinical impairment.

RADIOGRAPHIC PATTERNS OF SARCOIDOSIS-ASSOCIATED PF

The diagnosis of sarcoidosis-associated PF is established by radiographic imaging. Historically, Scadding chest x-ray stages, representing patterns of parenchymal and hilar changes, were widely used to qualify the extent of pulmonary sarcoidosis. Volume loss, lung and hilar distortion, and/or fibrocystic changes define fibrotic sarcoidosis and Scadding stage IV. In recent years, high resolution computed tomography (HRCT) has emerged as a more sensitive modality by which to identify fibrotic changes[9,10] Compared with chest x-ray stages, HRCT findings in sarcoidosis correlate better with pulmonary function and long-term prognoses.[11] However, similar to finding scant fibrosis on histology, small areas of fibrosis on HRCT may be physiologically incidental, and pathologically distinct from an extensive fibrotic process. The lack of standardized diagnostic criteria, radiographic or otherwise, to define clinically relevant pulmonary fibrosis in sarcoidosis has limited our ability to classify and study this phenotype.

Three HRCT patterns of sarcoidosis-associated PF have been described: bronchial distortion, diffuse linear, and honeycombing fibrosis (Fig. 1).[11] Bronchial distortion is marked by bronchial dilatation and angulation. A central location may predominate, or the distribution of bronchial changes may be diffuse. The extent to which bronchial distortion represents simple traction bronchiectasis versus damage to airway architecture from sarcoid inflammation is not known. As sarcoid inflammation occurs primarily along lymphatic channels, which are dense within bronchovascular tracts, bronchial distortion is the most common HRCT pattern of sarcoidosis-associated PF.[11,12] The presence of scattered peripheral lines, translobular lines, and/or septal reticulation defines the second HRCT pattern of diffuse linear fibrosis. This pattern is the result of sarcoid inflammation within the lymphatics that course through interlobular septa. Finally, honeycombing fibrosis defines the third radiographic pattern of sarcoidosis-associated PF. Honeycomb cysts occur at the distal airway and alveolar level. This is the least common HRCT pattern, observed in less than half of patients with sarcoidosis-associated PF. It is worth noting that while one pattern may predominate in a given patient, many patients have an overlap of fibrotic patterns.[11]

CLINICAL FINDINGS IN SARCOIDOSIS-ASSOCIATED PF

Consistent with findings in other fibrotic lung conditions, pulmonary function tests in sarcoidosis-associated PF often reveal restriction. However, given the peribronchial distribution of lesions in sarcoidosis, obstruction can also be evident, and a mixed pattern of restriction and obstruction is common.[11,13] Radiographic patterns may correlate with clinical outcomes. Patients with bronchial distortion may suffer from chronic bronchiectasis symptoms.[4] *Aspergillus mycetoma* can develop within lung cavities and fibrocystic lesions,