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The Pathogenesis of Pulmonary Sarcoidosis and Implications for Treatment

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Thoracic sarcoidosis is the most common form of sarcoidosis, encompassing a heterogeneous group of patients with a wide range of clinical features and associated outcomes. The distinction between isolated thoracic lymphadenopathy and pulmonary involvement matters. Morbidity is often higher, and long-term outcomes are worse for the latter. Although inflammatory infiltrates in pulmonary sarcoidosis may resolve, persistent disease activity is common and can result in lung fibrosis. Given the distinct clinical features and natural history of pulmonary sarcoidosis, its pathogenesis may differ in important ways from other sarcoidosis manifestations. This review highlights recent advances in the pathogenesis of pulmonary sarcoidosis, including the nature of the sarcoidosis antigen, the role of serum amyloid A and other host factors that contribute to alterations in innate immunity, factors that shape adaptive T-cell profiles in the lung, and how these mechanisms influence the maintenance of granulomatous inflammation in sarcoidosis. We discuss questions raised by recent findings, including the role of innate immunity in the pathogenesis, the meaning of immune cell exhaustion, and mechanisms that may contribute to lung fibrosis in sarcoidosis. We conclude with a reflection on when and how immunosuppressive therapies may be helpful for pulmonary sarcoidosis, a consideration of nonpharmacologic management strategies, and a survey of potential novel therapeutic targets for this vexing disease.

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Sarcoidosis is a systemic disease marked by sterile granulomatous inflammation in affected organs. The cause remains uncertain, but a constellation of archetypical clinical and immunologic features characterize the disease.[1] Although sarcoidosis can affect nearly any organ in the body, thoracic disease, when it includes lymphadenopathy, is the most common site. Although a global disease, the prevalence of sarcoidosis varies by ancestral background.[2] In the United States, a nationwide survey of a medical database found a prevalence of 60 per 100,000 adults, with a threefold higher rate in blacks compared with whites, and a low prevalence among Hispanics and Asians.[3]

The diagnosis of sarcoidosis is established by a combination of histopathologic and clinical findings.[4] Although many patients enter clinical remission within a few years of

ABBREVIATIONS: IFN = interferon; NLR = nucleotide-binding oligomerization domain-like receptor; SAA = serum amyloid A; Th = T helper; TLR = toll-like receptor; TNF = tumor necrosis factor; Treg = regulatory T

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diagnosis, approximately a third experience chronic disease. Long-term outcomes relating to morbidity and mortality are closely linked to clinical phenotypes. The acute presentation of hilar lymphadenopathy, called Löfgren syndrome when occurring with fever and erythema nodosum, typically confers an excellent prognosis. Outcomes are generally less favorable for parenchymal pulmonary sarcoidosis compared with lymph node limited disease (Table 1). In a recent study, relapsing disease was most common among patients with pulmonary involvement.[5] In addition, pulmonary parenchymal sarcoidosis can progress to pulmonary fibrosis, with its attendant respiratory impairment and secondary complications, including pulmonary hypertension and aspergillosis.[6]

Improving outcomes in sarcoidosis requires a better understanding of the pathogenesis. Fortunately, this is a dynamic period in sarcoidosis research. Several recent publications have started to challenge long-held assumptions about the pathophysiology. Further, a variety of recent publications clarify findings associated with the particularly common and morbid phenotype of pulmonary sarcoidosis. This review summarizes these findings. Specifically, we highlight the results of studies relating to antigen presentation, innate and adaptive immune responses, and granuloma biology in pulmonary sarcoidosis. The application of these findings to outcomes of chronic inflammation and pulmonary fibrosis is explored. We conclude with a discussion of clinical management and potential novel therapeutic domains.

Immunopathogenesis of Pulmonary Sarcoidosis

Pulmonary sarcoidosis is a highly orchestrated immune response involving, sequentially, antigen-driven CD4+ T-cell activation, chemokine-driven recruitment of activated T cells to the lung, local macrophage accumulation, and granuloma formation (Fig 1). Although macrophages may assume antigen presenting capabilities in the lung, dendritic cells traffic to regional lymph nodes for the initial presentation of antigen, leading to activation of quiescent circulating CD4+ lymphocytes.[7] A defining feature of active sarcoidosis is the dominant expression of interferon (IFN)-gamma in affected organs; IL-2, IL-12, and tumor necrosis factor (TNF)-alpha are other important cytokines. The role of pulmonary-derived exosomes, extracellular vesicles of cellular material capable of promoting inflammation locally and distally, as biomarkers and as possible disease modifiers, is being explored.[8] Even as the antigen remains elusive, the clonal amplification of CD4+ T cells strongly supports the tenet that a pathogenic antigen contributes to disease. The resulting CD4+ T-cell alveolitis serves as a biomarker, closely tracking the rise and fall of disease activity.[9] Typically noncaseating and tightly formed, sarcoidosis granulomas are sterile and in the lungs primarily locate along lymphatic tracks (Fig 2).[10]

Antigen Considerations

The long-standing search to identify the sarcoidosis antigen continues. One hypothesis is that of

TABLE 1] Clinical Features of Pulmonary Sarcoidosis

Clinical Phenotype	Pulmonary Manifestations	Imaging Findings	Pulmonary Function
Inflammatory pulmonary sarcoidosis	• Exertional dyspnea, dry cough, chest tightness • Less common: chest pain, pleural rub	• Bilateral hilar adenopathy (often with calcifications) • Focal to extensive reticulonodular opacities along interlobular septa and bronchovascular bundles, upper zone predominant • Less common: diffuse ground glass opacities, pneumothorax, pleural effusion	• Often normal but mild to moderate obstruction, restriction, or a mixed pattern of disease may be present • Bronchial hyperreactivity
Fibrotic sarcoidosis	• Mild to severe exertional dyspnea, dry cough, chest tightness, hypoxemia • Less common: inspiratory crackles, bronchiectasis-related sputum production, hemoptysis related to infection with *Aspergillosis* species	• Faint reticulations to dense linear bands • Cystic lung disease, traction bronchiectasis, and airway distortion • Less common: extensive parenchymal destruction, mycetoma	• Restriction and decreased diffusion capacity common • Severity related to extent of structural lung disease and presence of coexisting pulmonary hypertension • Nonreactive airflow obstruction common when airway distortion is present