Severe Sarcoidosis

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KEYWORDS

• Sarcoidosis • Pulmonary fibrosis • Cardiac sarcoidosis

KEY POINTS

- The indications for initiating therapy in sarcoidosis can be broadly dichotomized as danger from disease and unacceptable loss of quality of life.
- Disease should be viewed as dangerous if it is already severe or if there is a high risk of major progression.
- A multidisciplinary approach is required to identify severe pulmonary disease, with the integration of symptoms, pulmonary function tests, and imaging findings.
- In stratifying risk for future progression to severe disease, duration of disease and short-term disease behavior should also be taken into account.
- Advanced imaging techniques may be helpful in risk stratification in both pulmonary and cardiac sarcoidosis.

INTRODUCTION

In sarcoidosis, the considerable variability in initial presentation, disease evolution, and outcome poses major problems in the formulation of a logical management strategy. The spectrum of disease ranges from asymptomatic imaging abnormalities, encountered as an incidental finding, to prominent symptoms due to systemic disease activity or major organ involvement. Pulmonary involvement (lung or mediastinal involvement) is evident in 90% to 95% of cases, and this is variably associated with respiratory and systemic symptoms, including fatigue, musculoskeletal symptoms, fevers, and weight loss. The natural history and treated course of disease are also highly heterogeneous, ranging from spontaneous remission to progressive pulmonary and extrapulmonary disease, associated with increased morbidity and mortality.[1,2] Respiratory failure is the most frequent cause of death in sarcoidosis, except in Japanese patients, who most commonly die from cardiac involvement.[3,4] Pulmonary hypertension (PH) is an independent predictor of mortality in sarcoidosis, irrespective of specific organ involvement.[5]

Optimal management in sarcoidosis is critically dependent on the clarity of definition of treatment goals. The historical view that all patients with sarcoidosis require therapy was never uniformly accepted and is now widely regarded as wholly inappropriate. However, the indications for initiating therapy are not exact: clinicians less accustomed to managing sarcoidosis are confronted, in many texts, by a long list of indications for treatment but no logical overview of broad treatment objectives readily understood by patients. It has recently been suggested that clinical reasoning in this context should be based on a simple dichotomy of danger from disease and unacceptable loss of quality of life,[6] with the latter not considered further in this review. It can be argued that when disease is not overtly dangerous, decisions on treatment of morbidity should be patient-driven because the impact of symptoms on

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overall quality of life is something that can never be fully grasped by anyone other than the patient and immediate family. However, when there is danger from disease (consisting of a higher risk either of mortality or disability due to major organ involvement) present in a minority of cases, the management strategy should ideally be based on medical expertise and the identification of severe disease or of risk factors predictive of progression to severe disease. Although factors associated with a high likelihood of spontaneous remission have been clearly identified, including erythema nodosum, stage I chest X-radiographic abnormalities, and ocular involvement, stratification for a high risk of future severe disease is relatively imprecise.

Although the age-adjusted mortality is relatively low in sarcoidosis (2.8 per 1 million population from 1999 to 2010),[7] with less than 10% of patients having a reduction in life expectancy due to sarcoidosis, it is critically important to identify such patients as early as possible, but this is often far from straightforward. There is no classification of disease severity in sarcoidosis and no formal definition of severe sarcoidosis. In principle, severe disease might reasonably be classified according to the level of major organ involvement, but this approach has drawbacks. Intensive treatment algorithms centered on the presence of severe disease amount to an admission of defeat, with an implicit inability to anticipate progression to severe disease and initiate a vigorous approach earlier in the disease course. Ideally, patients at high risk of a malignant outcome should be identified at presentation or early during follow-up, based on (a) symptoms that might presage life-threatening manifestations such as sudden cardiac death or significant functional impairment interfering with essential aspects of daily life; (b) the staging of disease severity based on functional tests and imaging modalities, which have established prognostic significance[8,9]; and (c) the careful observation of longitudinal disease behavior with or without initial therapy.

The purposes of this review are first to detail the evaluation of disease severity in patients with pulmonary and cardiac sarcoidosis (because other less prevalent organ involvement, covered in-depth elsewhere in this issue, are less frequent indications for prolonged therapy). Prognostic evaluation to stratify risk, even when disease is not yet overtly severe, is also discussed. Treatment considerations in high-risk patients are detailed. The effect of age, race, and gender on risk and disease severity is not covered in-depth in this review, although also relevant to disease severity and mortality in sarcoidosis.[3,10]

SEVERE PULMONARY INVOLVEMENT

In most patients with sarcoidosis, disease is either self-limited with spontaneous remission, as typically seen in Löfgren syndrome, or treatment is rapidly effective and the long-term outcome is good. However, interstitial lung involvement progresses to significant pulmonary fibrosis in up to a third of cases.[11] Extensive interstitial lung disease with pulmonary fibrosis and PH has been strongly associated with increased morbidity and mortality. PH may develop as a complication of the severe pulmonary fibrosis but also may be evident without significant parenchymal involvement due to pulmonary vascular infiltration and other pathophysiological mechanisms.

The Definition of Severe Pulmonary Fibrosis

The presence of pulmonary fibrosis does not, in itself, result in differences in the range of clinical manifestations of lung involvement, which include cough, shortness of breath, wheeze, and episodes of hemoptysis (especially when Aspergillus and other fungal species have infiltrated segments with bronchiectatic or bronchial distorted areas). Interestingly, inspiratory crackles and clubbing are not present, in contrast to idiopathic pulmonary fibrosis (IPF).[12] A mixed ventilatory defect pattern with moderate to severe impairment in gas transfer is most common in patients with pulmonary fibrosis in sarcoidosis.[13] Airflow limitation is caused by both airway involvement with predominant inflammation of the small airways and, in an important subgroup, extensive fibrotic abnormalities. Staging the severity of pulmonary fibrosis requires confirmation that irreversible interstitial lung disease is present (based on imaging findings or lack of responsiveness to therapy) and the integration of symptoms, pulmonary function tests (PFT), and imaging findings.

It should be stressed that pulmonary disease severity cannot be staged with confidence without the integration of the above mentioned 3 domains, each of which is seriously flawed when considered in isolation. With regard to severe disease in particular, it might be supposed that exercise intolerance should drive treatment decisions, but although this may be broadly correct on quality-of-life grounds, exertional dyspnea does not always correlate with the severity of lung disease. A discussion of the multiplicity of thoracic and extrathoracic causes of exercise limitation in sarcoidosis lies beyond the scope of this review: suffice it to say that disability due to dyspnea may equally result from interstitial lung disease, PH, and cardiac sarcoidosis, in isolation or in combination. Pulmonary function severity thresholds

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