Fibrotic Pulmonary Sarcoidosis

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KEYWORDS

• Granuloma • Fibrosis • Progression • Morbidity • Mortality

KEY POINTS

- In sarcoidosis, fibrosis results from granulomatous inflammation.
- Fibrotic pulmonary sarcoidosis (fPS) affects about 20% of patients and is associated with an increased mortality.
- The prognosis of fPS is highly variable among patients and mainly depends on the extent of fibrosis, the severity of functional impairment, and the development of pulmonary hypertension.
- Most patients with fPS have persistent granulomatous activity, which is best detected by high-resolution computed tomography and 18 fluorodeoxyglucose positron emission tomography, and help guide the decision to initiate or reinforce anti-inflammatory treatment.
- The proportion of patients with progressive self-sustaining fibrosis that may benefit from antifibrotic treatment remain unknown.

INTRODUCTION

Although sarcoidosis is generally viewed as a benign disease, its prognosis is highly disparate according to ethnic and genetic factors, geographic origin, initial presentation, and organ involvement.[1–3] Although sarcoidosis generally resolves spontaneously in less than 2 years, a substantial proportion of patients present a chronic course, and a subgroup will sustain permanent sequelae in relation to the development of fibrosis (pulmonary and extrapulmonary).[1–3] Before the advance of high-resolution computed tomography (HRCT), fibrotic pulmonary sarcoidosis (fPS) was referred to as stage IV on chest radiography.[4–6] Radiographic stage IV usually develops after 5 years or more of disease and affects about 5% of patients at presentation and 20% during follow-up.[4–6] FPS is generally associated with loss of quality of life (QoL) and carries a significant morbidity burden and an excess mortality.[4–6] However, the presentation and evolution of fPS are extremely variable among affected patients, from asymptomatic or stable disease to inexorably progressive disease despite treatment and death. Patient outcomes mainly depend on the extent of fibrosis, the severity of functional impairment, and the development of pulmonary hypertension (PH) but are also influenced by several other comorbidities/complications, including infections or drug-induced toxicities.[4–6]

There has been considerable improvement in our comprehension of the pathogenesis of fibrosis in sarcoidosis during the last years but fPS remains a major challenge to clinicians.[4–6] In fact, even though it is admitted that fibrosis results from granulomatous inflammation, the inflammatory process may have disappeared at the moment of patient presentation. Thus, apart from treating comorbidities/complications, clinicians have to identify the

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Clin Chest Med 45 (2024) 199–212
https://doi.org/10.1016/j.ccm.2023.08.011
0272-5231/24/

patients who continue to have persistent granulomatous activity that may respond to anti-inflammatory treatment and those with irreversible self-sustaining fibrosis that may warrant antifibrotic treatment or lung transplantation.[4–6] This review tries to summarize the most recent literature on fPS, with a particular emphasis on pathogenesis and management in the light of the latest concept of progressive pulmonary fibrosis (PPF).

PATHOLOGY AND PATHOGENESIS OF FIBROTIC PULMONARY SARCOIDOSIS

The natural history of pulmonary fibrosis in light of sarcoid granulomas is still poorly understood. Based on histopathology studies and on Kveim's test biopsies,[7] it is hypothesized that at first a still unknown antigen is the trigger of an interstitial inflammation and alveolitis,[8–10] leading to granuloma formation with lymphatic distribution and airway involvement. The granulomatous inflammation will either disappear or persist and in some cases will have an evolution to fibrosis. One of the characteristics of pulmonary granulomas in sarcoidosis is to be mostly surrounded by a concentric rim of lamellar collagen bundles. This peripheral fibrosis may progress to complete hyalinization of the granuloma and extension into the lung parenchyma. In addition, the fibrotic rim enclosing granulomas consolidates the cohesiveness of granulomas aggregates[11,12] (**Fig. 1**A). The fibrotic process is usually the consequence of an activation and proliferation of fibroblasts and differentiation into myofibroblasts, leading to the production of extracellular matrix components such as collagen. Myofibroblasts, extracellular matrix components such as procollagen I and III or tenascin-C have been identified in the fibrotic rim enclosing granuloma suggesting an active fibrogenesis and matrix turnover in this area.[13]

In sarcoidosis, the mechanisms leading to the development of pulmonary fibrosis are not elucidated because very few studies directly compare the immune profile between patients with fibrotic sarcoidosis and those who do not progress to fibrosis. In fact, studies are mostly focused on the mechanisms of the early inflammatory/immune reactions or those associated with chronic active progressive sarcoidosis.[14]

The fibrotic process may be the continuum of granulomatous inflammation, with fibrotic changes predominantly occurring around granulomas[15] (**Fig. 1**B). However, current data do not allow to conclude whether lung fibrosis can occur distant from granulomatous inflammation and whether it depends on deregulation of repair, and/or whether persistent inflammation is required to induce progressive fibrosis.[16,17] Studies on lung explants from engrafted sarcoidosis patients mostly showed persistent granulomatous inflammation and a fibrosis pattern distinct from usual interstitial pneumonia (UIP), with a central fibrotic topography and absence of fibroblastic foci.[15,18,19] In addition, severe chronic interstitial pneumonitis may persist associated with more rapidly progressive forms.[20] However, at variance some reports of sarcoidosis lung explant examination showed features consistent with UIP pattern, including fibroblastic foci and patchy distribution,[18,20,21] which may suggest an aberrant reparative response associated with fibrosis in sarcoidosis. Interestingly, using microdissection of fibroblastic foci on lung explants from patients with idiopathic pulmonary fibrosis (IPF) and fPS, transcriptomic analysis showed similar profiles of fibrosis-related genes.[22] Another possibility is that some patients may develop a fibrotic lung disease distinct from sarcoidosis that accounts for the aspect of IPF, a hypothesis considered in recent clinical series.[23]

The biological and immune mechanisms that may explain fPS are more likely multiple (**Fig. 2**), encompassing changes in the profibrotic/antifibrotic homeostatic response (cytokine production and fibroblast and matrix regulation), an intense and chronic inflammatory response, a possible role of environment (*cf* infra) and microenvironment.

An increased level of profibrosing cytokines such as vascular endothelial growth factor (VEGF), platelet-derived growth factor-AB (PDGF-AB), and fibroblast growth factor-2 (FGF-2) were found in sera from fPS.[24] The role of transforming growth factor-beta (TGF-ß), one of the major cytokine involved in fibrosis and repair but also having anti-inflammatory function, is unclear. High expression of TGF-ß or polymorphism of *TGFB1* may be found in patients with a good prognosis of their sarcoidosis.[25–27] By contrast, polymorphisms of *TGFB3 or GREM1* (gremlin1 that may regulate TGF-ß) may be associated with fPS.[28,29] Interestingly, in patients with pulmonary sarcoidosis, blood Th17 PD-1+ TCD4+ lymphocytes are the major source of TGF-ß among TCD4+ cells, dependently of the transcription factor signal transducer and activator of transcription 3 (STAT3). Coculture of these Th17 PD-1+ TCD4+ lymphocytes with human lung fibroblasts induces collagen-1 production.[30] This suggests that Th17 response in sarcoidosis may be significant in fPS, by inducing TGF-ß secretion leading to fibroblast activation. Moreover, sarcoid lung fibroblasts display a high proliferative activity and secretion of profibrotic cytokines as interleukin (IL)-6.[31] In

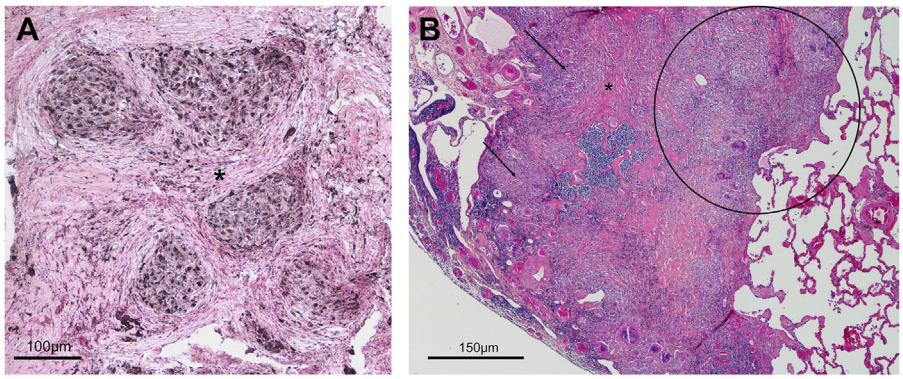

Fig. 1. Pathologic findings in patients with fibrotic pulmonary sarcoidosis. (*A*) Immunohistochemistry of CD68 expression (an epithelioid and macrophages marker) in a lung biopsy from a patient with a fibrotic pulmonary sarcoidosis showing granulomas wrapped by a dense fibrosis (*asterisk*) consolidating cohesiveness of granulomas aggregates. (*B*) Lung explant from a patient engrafted for a fibrotic pulmonary sarcoidosis. Hematoxylin and eosin staining showing granulomas and lymphocytes highlighted by the circle and pointed by arrows, associated with dense fibrosis. (Acknowledgment: Dr Vincent THOMAS DE MONTPREVILLE, Marie-Lannelongue Hospital Le Plessis Robinson France.)

addition, high levels and increased activity of matrix metalloproteinases that regulate the extracellular matrix turnover and influence the activation of myofibroblasts have been reported in bronchoalveolar lavage (BAL) from fPS.[31]

An M2/Th2 transition is another hypothesis explaining evolution to fibrosis in sarcoidosis.[16] Alternatively, activated macrophages or M2-like are anti-inflammatory and associated with repair and fibrosis. Alveolar macrophages from patients with fPS produce more CCL18, especially if they have been activated by Th2-like cytokines, resulting in an M2-like phenotype.[32] CCL18 is thought to have a profibrosing action by stimulating collagen production by fibroblasts.[32]

Furthermore, chronic granulomatous inflammation may favor fibrosis. The uninhibited mammalian target of rapamycin (mTOR) signaling pathway, potentially in lung macrophages, could be important in chronic granulomatous inflammation.[33] The mTOR complex 1 (mTORC1) regulates the metabolism and proliferation of many cells, including Th1, Th17 lymphocytes. An abnormal interaction between mTOR and autophagy has been proposed to impair antigen clearance and promote the progression of granulomas.[34]

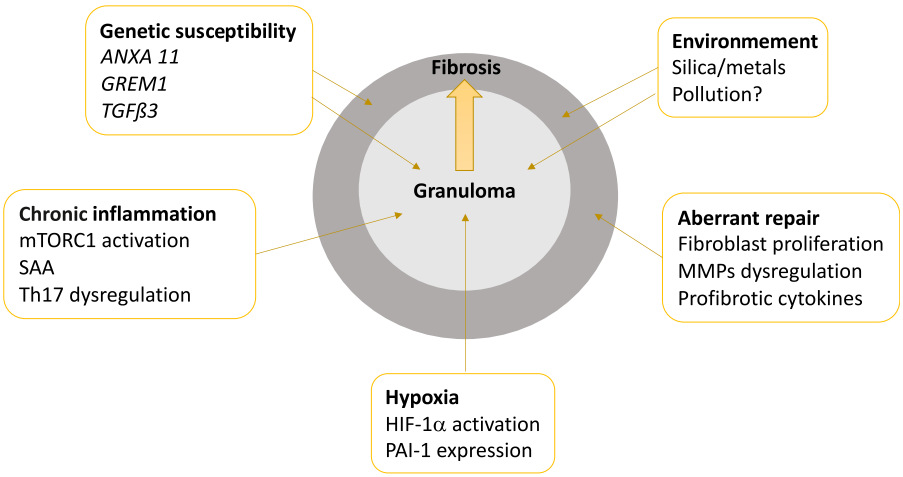

Fig. 2. Possible factors associated with fibrotic pulmonary sarcoidosis that may directly affect fibrosis or via granulomatous inflammation. ANXA11, annexin 11; GREM1, gremlin 1; HIF, hypoxia inducible factor 1; MMPs, matrix metalloproteinase; mTORC1, mammalian target of rapamycin complex 1; PAI-1, plasminogen plasminogen activator inhibitor-1; SAA, serum amyloid A; TGF, transforming growth factor.

Recently, in bulk RNA sequencing of BAL cells comparing stage 1 to stage 4 sarcoidosis, mTORC1 gene sets were found upregulated, as cell cycle, IL-6, IL-8, and IL-1 signaling.[35] Annexins (ANX) are a large family of calcium-dependent membrane-binding proteins that play critical functional role in the cell life cycle and apoptosis. In an African-American cohort followed-up for at least 2 years, a minor allele of *ANXA11* was observed associated with fPS.[36] The pathogenic effect of *ANXA11* variant might be due to a defective apoptosis inside granuloma thus inducing a persistent inflammatory reaction.[37]

Serum amyloid proteins (SAA) are acute phase response proteins secreted by the liver but that could potentially be locally expressed in macrophages.[38] SAA may bind to TLR-2 of various cells in the lung of patients with sarcoidosis causing production of IFN-γ, TNF, and IL-18 that could possibly activate Th17 lymphocytes.[39] SAA immunostaining in lung samples from fPS, correlated with the collagen deposition.[39] Beijers and colleagues found that patients with radiographic stage 4 had higher serum SAA levels compared with patients with sarcoidosis without fibrosis. SAA levels in sera were also increased in other fibrotic diseases such as in patients with IPF associating SAA levels to fibrosis rather than to sarcoidosis per se.

Absence of in-depth vascularization in pulmonary sarcoid granuloma and hypermetabolism of inflammatory cells suggest that immune cells in sarcoidosis are exposed to hypoxia.[40] The cellular response to hypoxia is mostly controlled by the hypoxia-inducible factor 1-α (HIF-1α) transcription factor that induces transcription of target genes such as the profibrotic factor plasminogen activator inhibitor-1 (PAI-1). Jeny *and colleagues* found that HIF-1α and PAI-1 were expressed in the center of granulomas, and that monocyte-derived macrophages from active pulmonary sarcoidosis showed a high HIF-1α transactivity and secreted a high level of PAI-1 inhibiting the migration of lung fibroblasts Therefore, hypoxia could favor fibrosis by promoting profibrotic cytokines response and by sequestering fibroblasts in the vicinity of granulomas via PAI-1.[41]

RISK FACTORS AND CLINICAL PRESENTATION OF FIBROTIC PULMONARY SARCOIDOSIS

In about two-thirds of cases, fPS is recognized after a long follow-up, whereas for the remaining one-third, it reveals the disease.[4–6] There is no case-control study focusing on the risk factors for developing pulmonary fibrosis in sarcoidosis. It has been suggested that stage IV disease is more frequent in Afro-American patients.[42] In the French retrospective cohort by Nardi and colleagues on 142 stage IV patients, the average duration of sarcoidosis was 5.8 $\pm$ 6.2 years.[43] There was a slight male predilection (52.1%), with a higher than expected proportion of Blacks (31.7%) and a mean age of 48.1 $\pm$ 12 years at stage IV presentation.[43] Initial manifestations included dyspnea (80%), chronic cough (51.4%), sputum (20%), and exceptionally hemoptysis (2.8%). Crackles, wheezing, and digital clubbing were present in 28.2%, 5.6%, and 6.3% of patients, respectively. Sarcoidosis was confined to the lungs in 26.4%.[43]

The implication of air pollutants in the development and progression of pulmonary fibrosis has been rarely examined in sarcoidosis. Recently, a significant association was found between exposure to inorganic dust, such as metal or silica dust, and sarcoidosis limited to lungs and/or intrathoracic lymph nodes (OR: 2.11; 95% CI: 1.11–4.17),[44] and an immunoreactivity to silica and metals was associated to fPS.[45] Liu and colleagues found that occupational metals exposure was a risk factor for death in sarcoidosis (OR: 1.41; 95% CI: 1.08–1.85).[46] Lower levels of education and incomes and the absence of private health insurance may be associated with a more severe pulmonary disease, as defined by radiographic stage, lung function measurements, and the use of supplemental oxygen.[47,48]

IMAGING OF FIBROTIC PULMONARY SARCOIDOSIS

More than 5 decades ago, Scadding classified postero-anterior chest radiography findings into 5 stages: stage 0 (normal), stage I (bilateral hilar lymphadenopathy [BHL]), stage II (BHL accompanied by pulmonary infiltrates), stage III (pulmonary infiltrates without BHL), and stage IV (overt pulmonary fibrosis).[1–3] A major shortcoming with this classification is the poor reproducibility of reading, in particular for the attribution of stage IV.[49,50]

HRCT is much more sensible than chest radiography for detecting pulmonary fibrosis.[51] Lung architectural distortion is constant in stage IV disease and, overall, is reported in 20% to 50% of patients with sarcoidosis.[51] It includes abnormal displacement of hila, fissures, bronchovascular bundles, and distorted septal lines. Posterior displacement of the main or upper lobe bronchus and volume loss (particularly in the posterior segment of upper lobes) are characteristics of fPS. Bronchi may be deformed, angulated, crossed, or stenosed. Conglomerate masses often

surround and encompass the bronchi and vessels. They are usually central and associated with bronchial distortion.[51] Other features of fPS are linear opacities radiating from the hila, traction bronchiectasis, honeycombing, and other types of cystic destruction, bullae and para-cicatricial emphysema, which are encountered mainly in mid/upper areas.[51,52] The picture of "advanced" fPS has been previously designated as "fibrocystic" pulmonary sarcoidosis.

In the study by Abehsera and colleagues on 80 stage IV patients, 3 distinct HRCT patterns of fibrosis could be separated with a very good interobserver agreement[53]: the bronchial distortion pattern (47% of patients), with or without coexistent masses (**Fig. 3**A, C); the honeycombing pattern (29%) (**Fig. 4**); and the linear pattern (24%) (**Fig. 5**). These patterns were associated with different functional profiles (see later discussion). Because the patterns usually do not overlap, it suggests different pathogenesis.[53] On serial HRCT images, ground-glass opacities and consolidations tend to evolve into honeycombing, whereas conglomeration masses shrank and evolve into bronchial distortion.[51,52]

When present in fPS, honeycombing follows the same distribution as granulomas. In contrast to UIP/IPF, it clearly predominates in upper lobes and in a perihilar and peribronchovascular distribution, with a trend to higher diameter of cysts[15,51,52] (see **Fig. 4**). Having said that, a pattern of UIP-like honeycombing can rarely be seen in sarcoidosis, with a striking prominence in the lower lung zones, a peripheral and subpleural distribution, or a diffuse distribution (see later discussion).[23,54,55] A pleuroparenchymal fibroelastosis-like pattern has also been described in a handful of cases, with a bilateral shrinkage of the upper lobes, pleural thickening, peripheral consolidations with traction bronchiectasis, and wedge-shaped opacities.[52]

LUNG FUNCTION IN FIBROTIC PULMONARY SARCOIDOSIS

Correlations between the radiographic staging and pulmonary function tests (PFTs) are imprecise, even though the degree of physiologic impairment generally increases in more advanced stages.[51] In the study by Nardi and colleagues, mean forced expiratory volume in 1 second (FEV1) was 63.9% of predicted value (pred), mean forced vital capacity (FVC) was 71.6% pred, mean FEV1/FVC was 73.4%, and mean diffusing capacity of the lung for carbon monoxide (DLCO) was 56.2% pred at stage IV presentation.[43] A restrictive, obstructive, and mixed ventilatory defect was observed in 63.2%, 36.1%, and 19.5%, respectively.[43] The British retrospective cohort by Kouranos and colleagues focused on the PFTs findings of 1100 patients with sarcoidosis, of whom 32.4% had stage IV disease.[56] As expected, the prevalence of stage IV was significantly lower in patients with normal ventilatory patterns. Stage IV disease was more frequently associated with a mixed ventilatory defect than obstructive or restrictive defects.[56]

The degree of physiologic alteration is usually linked to an overall HRCT score of sarcoidosis lung involvement but most correlations are weak, and there is no study focusing specifically on correlations between the extent of fibrosis and PFT in fPS.[51] The composite physiologic index (CPI), a weighted index of pulmonary function variables originally devised for IPF, confers increased sensitivity to concurrent emphysema and PH, whereas at the same time capturing the prognostic effect of interstitial lung disease (ILD). CPI has demonstrated its prognostic strength in pulmonary sarcoidosis,[57–59] including in those with fPS.[59]

Bronchial distortion pattern on HRCT is associated with lower expiratory airflow rates, whereas honeycombing pattern is associated with restriction and lower DLCO, and functional impairment is relatively minor when linear pattern predominates.[53]

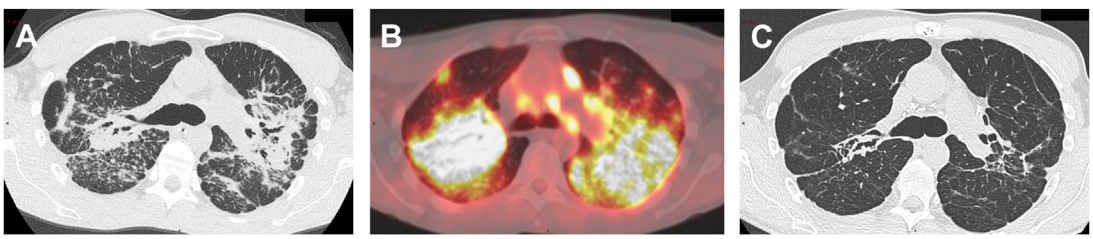

Fig. 3. A 50-year-old man with fibrotic pulmonary sarcoidosis with a pattern of distortion and mixed ventilatory defect. HRCT scans show a pattern of distortion in the upper lobes, with posterior and superior displacement of the main bronchus and angulated and deformed airways (*A, C*). Superimposed peribronchovascular and septal thickening, ground-glass opacification and nodules suggest the presence of persistent granulomatous activity (*A*), which was confirmed by the intense uptake of ^{18}FDG on PET/CET (*B*). The features of granulomatous activity were reversible under treatment (*C*).

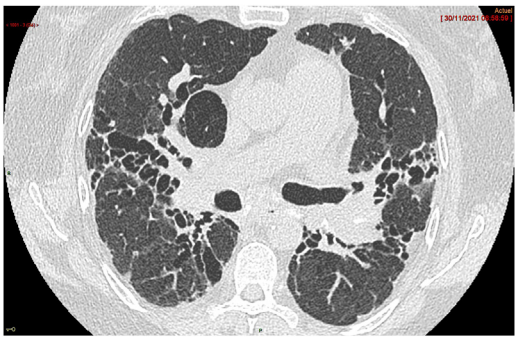

Fig. 4. A 63-year-old woman with fibrotic pulmonary sarcoidosis with a pattern of honeycombing, severe restrictive defect, and PH. HRCT scan shows a pattern of honeycombing, with cysts of various sizes that predominate in the upper and perihilar regions, and along the bronchovascular bundles. Note that the MPAD/ascending aorta diameter ratio is > 1.

EVALUATION OF PERSISTENT GRANULOMATOUS INFLAMMATION IN FIBROTIC PULMONARY SARCOIDOSIS

In fPS, fibrosis can be isolated or associated with additional granulomatous process, which is critical to guide therapeutic decisions. As elegantly formulated in an editorial by Judson and colleagues, subtle granulomatous inflammation, described as "smouldering sarcoidosis" in that it is not the cause of acute symptoms or organ dysfunction but is still a possible source of further fibrosis, may escape detection.[60] Detection of such subtle granulomatous inflammation may require multimodal assessment, including worsening pulmonary symptoms or function, elevation of serum or BAL biomarkers, worsening imaging, and HRCT or metabolic features of disease activity. The problem is that all of these methods have at least one of the following flaws: low sensitivity, low specificity, lack of standardization and significant cost.[60]

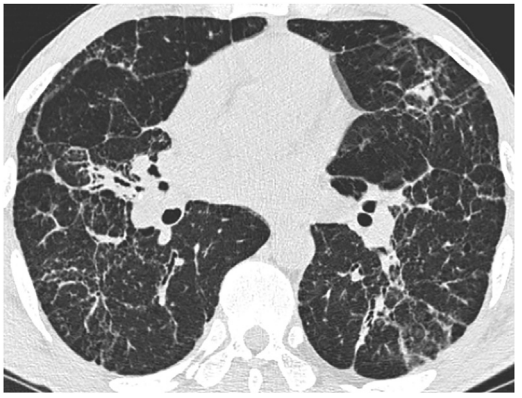

Fig. 5. A 55-year-old man with fibrotic pulmonary sarcoidosis with a linear pattern, and normal lung function. HRCT scan shows a linear pattern, with diffuse linear opacities that are distorted and radiate from the hila.

In the study by Nardi and colleagues, most stage IV patients displayed signs of persistent disease activity, as judged by increased serum angiotensin-converting enzyme (SACE; 59.7%) and lymphocytosis on BAL (64.4%).[43] Functional improvement was noted in 38.6% of treated patients. However, SACE levels and lymphocytosis failed to predict improvement, suggesting the futility of these investigations in this context. Patients who improved differed from those who did not improve for a shorter duration of sarcoidosis.[43]

HRCT is helpful for discriminating between active inflammation and irreversible fibrosis[51] (**Table 1**, see **Fig. 3**A, C). Benamore and colleagues analyzed the HRCT scans of 100 sarcoidosis patients regarding several abnormalities known to be, at least partially, indicative of active inflammation, and correlated the extent of each of them against several surrogates of disease activity (SACE and sIL-2R levels, and changes in FVC).[61] HRCT extent scores for nodularity, ground-glass opacification, interlobular septal thickening, and consolidation but not conglomeration or intrathoracic lymphadenopathy, correlated significantly with at least one of the disease activity parameters and were used to form an activity score. The sum of these 4 scores, CTAS, was highly reproducible between radiologists.[61] Patients with fibrosis had higher CTAS compared with those without fibrosis, and, importantly, CTAS was found to predict the size of FVC response to treatment at 1 year, not only in the nonfibrotic but also the fibrotic subgroup.[61]

It is now admitted that 18 fluorodeoxyglucose (^{18}FDG) uptake on positron emission tomography/CT (PET/CT) is associated with sarcoidosis activity, and predicts therapeutic response.[62] However, only few publications have focused on ^{18}FDG-PET in fPS. In a study by Mostard and colleagues on 95 patients with sarcoidosis, 22 out of 26 patients (85%) with pulmonary fibrosis had positive pulmonary ^{18}FDG-PET findings, with a median SUVmax of 7.1.[63] Positive extrapulmonary ^{18}FDG-PET lesions were shown in 18 out of 22 patients (82%) and positive combined serologic inflammatory testing in 16 out of 22 patients (73%).[63] Although ^{18}FDG-PET/CT tends to supplant HRCT for determining residual inflammation in fPS (**Fig. 3**B), the added role of ^{18}FDG-PET for treatment decisions needs to be clearly established in longitudinal studies.

Table 1
Reversibility of sarcoidosis features observed on computed tomography (spontaneously or under treatment)

Reversible Features	Irreversible Features	Variable Reversibility
Micronodules	Architectural distortion	Consolidation [a]
Nodules	Bronchial distortion	Ground-glass opacification [b]
Peribronchovascular thickening	Conglomeration masses	Linear opacities, including septal lines [c]
	Honeycombing	
	Bullae	

[a] Consolidations are wholly or partially reversible in most cases, in particular those with surrounding micronodules, representing coalescent granulomas.
[b] A coarse texture or concomitant traction bronchiectasis increases the likelihood of underlying fibrosis.
[c] Irregular distorted lines are more likely to be fibrotic.

FIBROTIC PULMONARY SARCOIDOSIS WITH USUAL INTERSTITIAL PNEUMONIA-LIKE PATTERN

The radiological and pathologic pattern of fPS is usually very dissimilar from that of UIP/IPF.[15,51,52] Noticeably yet, UIP pattern on HRCT, with pathologic evidence of isolated UIP or UIP-like pattern with concomitant granulomas, has been rarely described in small series of patients with fPS.[20,21,23,54,55,64] Collins and colleagues reported 25 patients with so-called combined sarcoidosis and IPF (CSIPF), as defined by clinical, radiological, and pathologic features of both sarcoidosis and IPF.[23] Most patients with CSIPF had an earlier diagnosis of sarcoidosis but 7 (28%) were diagnosed simultaneously with both conditions. There was a majority of men (68%), Caucasians (84%), smokers (56%), and 16% had a familial history of pulmonary fibrosis. Mean age was 54.2 and 63.6 years at sarcoidosis and IPF diagnosis, respectively. A UIP pattern was revealed in most patients (68%), whereas the pattern was "possible" UIP (24%) or "inconsistent with UIP" (8%) in a minority.[23] Pathologic specimens from surgical lung biopsy, explanted lung, or autopsy were available for 17 patients with CSIPF, and of those, 12 patients (70.6%) had features of granulomas and UIP in different areas of the lungs. The annual functional decline after CSIPF diagnosis was similar to that of lone-IPF, as was survival, with a mean survival of 3.2 years.[23] The particular frequency of a familial history of pulmonary fibrosis has been underlined by other authors as well as the possible role of occupational exposure.[55] This association is intriguing, and whether CSIPF results from the de novo development of a second lung disease or fibrosis progresses to a particular phenotype of UIP in genetically predisposed patients remains unknown.[65–67]

COMPLICATIONS DURING THE COURSE OF FIBROTIC PULMONARY SARCOIDOSIS

Patients with fPS can exhibit several types of complications that commonly induce QoL impairment and are potentially life threatening.[4–6] In the study by Nardi and colleagues, during the follow-up period of 7.1 $\pm$ 4.8 years, PH was observed in 29.7% of cases and chronic aspergillosis in 11.3%.[43] Pneumothorax occurred in 8.5% of patients and relapsed in one-third. Other complications included *mycobacterium* infections (9.1%), pneumonia (7%), pulmonary embolism (5.6%), and acute respiratory failure requiring admission to an intensive care unit (5.6%). Long-term oxygen was prescribed to 12% of patients.[43]

The rate of serious infection is increased 1.8-fold in sarcoidosis compared with the general population.[68] This risk is further increased within the first 2 years of follow-up and under immunosuppressive treatment,[68] in particular azathioprine,[69] cyclophosphamide,[70] or antitumor necrosis factor (TNF)-α agents.[71] Over and above treatment and possible sarcoidosis-induced immunosuppression, local factors may be conducive to pulmonary infections in fPS, such as bronchiectasis and fibrocystic areas.[4–6] Almost all patients who develop chronic aspergillosis have fibrocystic pulmonary sarcoidosis.[72] These patients may have a high-risk occupational exposure to air molds and dusts.[72]

Patients with fPS are more likely to experiment acute exacerbations (AE), which can result from an infectious trigger or a true flare up of sarcoidosis.[73,74] Although these AE more closely resemble those encountered in chronic obstructive pulmonary disease (COPD) than in IPF, there is no consensual definition of AE in this context.[4–6] In a study by Baughman and colleagues on 129 patients with fPS, AE was defined as a worsening event treated with a limited course of either

antibiotics and/or increased corticosteroid doses, which resolved within 4 weeks. Ninety-four (73%) of patients reported a median of 3 events (range 0–8) in the prior year, and these were more common in those with bronchiectasis and those receiving anti-TNF-α agents.[74] Interestingly, in a small cohort of 16 patients with fPS, $PM_{2.5}$ exposure was associated with increased severity of respiratory and QoL symptoms but not with functional decline.[75]

FIBROTIC PULMONARY SARCOIDOSIS AND THE CONCEPT OF PROGRESSIVE PULMONARY FIBROSIS

There has been growing interest during the last years in the concept of PPF because these patients may benefit from antifibrotic treatment.[76] There is however no standard definition of fibrosis progression,[77,78] which is particularly problematic in fPS where worsening respiratory symptoms and functional deterioration can also be related to various other causes (relapse of the granulomatous process; airways involvement; cardiac involvement; PH; and corticosteroid-induced toxicity such as amyotrophy, infection, osteoporosis, and so forth).[4–6]

Typically, fPS progresses relatively slowly and can fluctuate.[4–6] In the study by Nardi and colleagues, the annual changes in lung function were marginal on average, with a variation of 1.4 $\pm$ 6.4% pred per year for FVC and 0.5 $\pm$ 9.1%pred per year for DLCO.[43] Long-term functional evaluation, performed with a mean interval of 6.2 $\pm$ 4.4 years, showed that PFTs were better in 39.3% of patients, stable in 35.9% and worse in 24.8%.[43]

In the large Canadian prospective registry by Hambly and colleagues including various fibrotic ILDs, 32% of 92 patients with sarcoidosis met progression criteria, which is surprisingly high.[79] Disease progression was defined as in INBUILD trial by a relative FVC decline of 10% or greater, death, lung transplantation or any 2 of within 24 months of follow-up: relative FVC decline of 5% or greater and less than 10%, worsening respiratory symptoms, or worsening fibrosis on HRCT. However, there was neither information on the radiographic stage nor fibrosis extent on HRCT at inclusion.[79] In the Dutch retrospective cohort by Schimmelpennink and colleagues including 106 patients with sarcoidosis with a DLCO less than 50% pred, 15% progressed based on a similar definition.[80] However, only 59% of patients demonstrated stage IV disease and 53% greater than 10% fibrosis on HRCT. Four (4%) patients had a UIP-like pattern on HRCT. Interestingly, there was no significant difference in MUC5B polymorphism between progressive and nonprogressive fPS. Patients with progressive fPS showed a worse survival.[80]

In INBUILD trial, which evaluated the effect of Nintedanib in FPF, fPS represented only 1.8% of all included patients.[81] In real-life cohorts of PPF, the proportion of patients with fPS ranges from 0% to 17% according to the criteria used to define progression.[79,80,82–86]

Currently, the factors associated with progression in fPS are unknown.[77,78] In a large international study by Le Pavec and colleagues, including 112 patients transplanted for advanced pulmonary sarcoidosis, several lung phenotypes were individualized: extended fibrosis only (17%); airflow obstruction (16%); severe PH and airflow obstruction; (17%); severe PH, airflow obstruction and fibrosis (14%); severe PH and fibrosis (11%); airflow obstruction and fibrosis (9%); severe PH (5%); and none of these criteria (11%).[87]

MORTALITY OF FIBROTIC PULMONARY SARCOIDOSIS AND PROGNOSTIC STRATIFICATION

Mortality risk is increased by 1.48 to 2.44-fold in patients with sarcoidosis as compared with the matched general population in Western countries,[43,88–90] and they also die younger.[89,91,92] This excess mortality is even more salient in non-Hispanic Blacks in the United States[91,93] and in patients requiring corticosteroids.[89,90]

Pulmonary fibrosis and its consequences are the main contributors to mortality.[4–6] According to death registries in the United States and France, the leading causes of death related to sarcoidosis are respiratory failure, pulmonary fibrosis and PH, followed by cardiovascular and infectious diseases.[92,94] In addition, radiographic stage IV portends a poorer survival in sarcoidosis.[56,58] Finally, lung fibrosis extent on HRCT has been consistently associated with a higher mortality in unselected patients with sarcoidosis[57,58] and in those with stage IV disease.[59] As such, CPI, main pulmonary artery diameter (MPAD) to ascending aorta diameter ratio, and an extent of fibrosis threshold of 20% have been combined to form an easily applied staging algorithm for determining prognosis in pulmonary sarcoidosis.[56–58]

In 2 studies including stage IV patients, survival was 91.5% to 94.4% at 5 years, 83.5% to 84.1% at 10 years, and 75.4% to 78.1% at 15 years.[43,59] At multivariate analysis, independent predictors of mortality were CPI, lung fibrosis extent, PH (as judged by echocardiography or MPAD/body surface area ratio), and geographic origin.[59]

MANAGEMENT OF FIBROTIC PULMONARY SARCOIDOSIS

The management of patients with fPS is complex and cannot be standardized.[4–6] The approach should be multidisciplinary and tailored for each patient, including not only anti-inflammatory treatment but also the treatment of comorbidities (aspergillosis, PH, and so forth) and symptoms, and, in highly selected cases with relentlessly progressive disease, antifibrotic treatment, and lung transplantation[4–6] (**Fig. 6**).

Although multiple lines of evidence suggest that fibrosis results from granulomatous inflammation, the role of anti-inflammatory treatment in ultimately altering the natural history of pulmonary sarcoidosis is debated.[4–6] The large majority of patients with fPS have been previously treated unsuccessfully with corticosteroids and multiple immunosuppressants.[43,59] Once pulmonary fibrosis is established, the decision to initiate, continue or escalate potentially harmful treatment is often tricky.[4–6] Indeed, even though pulmonary fibrosis is associated with a higher risk for death or respiratory dysfunction and impaired QoL, not all patients with fPS justify treatment. First, the caveat is that respiratory dysfunction can be related to irreversible organ damage.[4–6] Resolution of the granulomatous inflammation should arrest the development of pulmonary fibrosis but the anti-inflammatory treatment will be inactive in burnt-out disease. Second, QoL can be impaired for several reasons, including comorbidities or drug-induced toxicities.[4–6] Thus, therapeutic decisions should be individualized and integrate the presence of disabling symptoms, the level of functional alteration or functional decline over time, evidence of ongoing granulomatous inflammation (see above), and the risk of treatment. If anti-inflammatory treatment is decided, its goals should be clearly stated (to achieve either improvement or stabilization or to prevent disease progression), as well as the instruments for assessing its effect (symptoms, lung function, or imaging).[4–6] Unfortunately, there is no specific recommendation for fPS in the ERS and BTS clinical guidelines on sarcoidosis on who, when, and how long to treat patients with fPS.[95,96] One should remember that fPS frequently requires prolonged treatment, with the risk of long-term cumulative toxicity of corticosteroids. However, the immunosuppressants

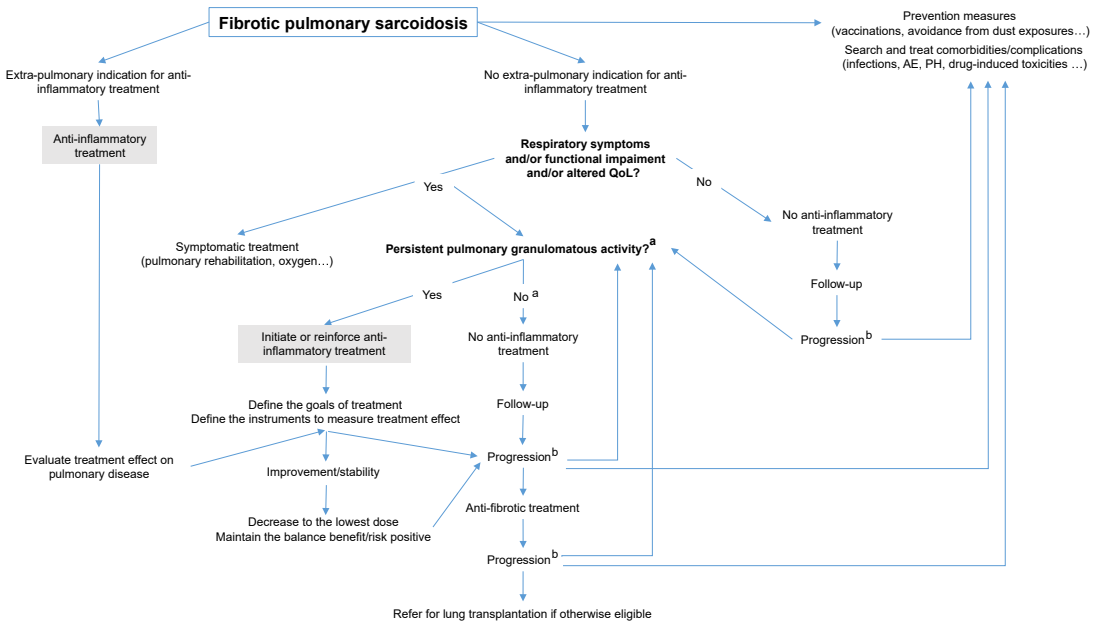

Fig. 6. Proposed algorithm for the management of patients with fibrotic pulmonary sarcoidosis.[a]The evaluation of persistent granulomatous activity is critical but often difficult and it primarily relies on HRCT and ^{18}FDG PET/CT. However, relevant inflammation may escape detection, and several authors advocate a trial of anti-inflammatory treatment in a minority of patients with uncertain findings on HRCT and mild ^{18}FDG uptake on PET/CT, on a case-by-case basis. [b]Clinical, functional, or radiological worsening may be due to several causes, including a flare-up of the granulomatous process, self-sustaining fibrosis, or various comorbidities/complications (infections, PH, drug-induced toxicities, and so forth). These need to be ruled out before concluding that there is a disease progression. There is no consensual definition of progressive fibrosis in patients with fibrotic pulmonary sarcoidosis. AE, acute exacerbation; PH, pulmonary hypertension; QoL, quality of life.

potentially precipitate infection in fPS, which in turn may stimulate further fibrosis.[4–6]

Despite encouraging results with antifibrotic agents for reducing the rate of decline in PPF,[76] little has been published in fPS. Theoretically, such therapy could be considered in patients with UIP-like pattern and in those with progressive disease despite adequate anti-inflammatory treatment.[4–6] The problem is that the rate the progression of fPS is unclear, and if progression is slow, it may be problematic to ascertain the benefit of antifibrotic treatment. Only 1.8% of all patients included in INBUILD trial had fPS, and no specific results are available.[81] A feasibility study showed that time to clinical worsening, and changes in DLCO and FVC did not differ significantly between pirfenidone (n = 11) and placebo (n = 5) in fPS at 18 months. However, the study was terminated prematurely due to the coronavirus disease 2019 pandemic and was underpowered to detect a difference between treatment arms.[97]

Interestingly, a small trial by Baughman and colleagues suggested that roflumilast, a phosphodiesterase-4 inhibitor, may reduce the incidence of AE at 12 months of follow-up compared with placebo in patients with fPS (n = 14 in each arm).[98] Pulmonary rehabilitation may be a complementary therapeutic intervention in fPS.[99,100] In order to prevent the development of chronic aspergillosis, it seems reasonable to recommend to the patients with fPS precautions to reduce mold exposure, including avoidance of gardening, spreading mulch, or close exposure to construction or renovation.[72]

Stage IV patients seem to have reduced daily life physical activity mainly because of compromised $V_{O_{2max}}$.[101] However, a randomized controlled trial by Wallaert and colleagues did not demonstrate a positive impact of such a program on daily life physical activity at 12 months, compared with counseling, in stage IV patients. Conversely, it did significantly increased exercise tolerance and decreased the dyspnea and fatigue scores.[102]

Pulmonary transplantation for fPS is performed infrequently but is effective, with results generally matching those of other diagnoses.[4–6] In the study by Le Pavec and colleagues, posttransplant survival rates were 86% and 69% at 1 and 5 years, respectively.[87] The main factors associated with worse survival were older age and extensive preoperative lung fibrosis.[87] Medical therapy should have been exhausted and sarcoidosis spread and activity have been carefully evaluated before referral.[4–6] The presence of aspergilloma should not definitely disqualify potential transplant candidate.[4–6]

FUTURE CHALLENGES AND PERSPECTIVES

Despite major progress in understanding the development of pulmonary fibrosis in sarcoidosis, fPS remains the subset of patients with greatest clinical need for better management strategies. Essential questions persist about the factors that lead to fPS, means for early recognition of patients at risk for fPS, and among them, those at risk for progression, and how to treat fPS and avoid progression. In order to delineate the respective place of anti-inflammatory and antifibrotic treatment and use appropriate outcomes in clinical trials, it would be highly desirable to find reliable biomarkers of residual granulomatous inflammation and to better outline what is disease progression in fPS, and the proportion of patients concerned.

CLINICS CARE POINTS

- Outcomes in fPS are highly variable- Pulmonary deterioration in fPS may have multiple causes, and should be investigated in the light of residual granulomatous activity, infection (particularly aspergillosis), and pulmonary hypertension.
- Assessment of pulmonary residual granulomatous activity is essential to guide therapeutic management.
- Patients with fPS should have a regular long term monitoring of their pulmonary function and cardiac ultrasound, as severity of functional impairment and pulmonary hypertension are major mortality factors.

DISCLOSURE

HN reports personal fees for steering committees, advisory boards, or consulting from Boehringer Ingelheim, and from Janssen, and reports grants to his institution from Boehringer Ingelheim, Kinevant and Atyr.

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