SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2023; 40 (3); e2023027 DOI: 10.36141/svdld.v40i3.14830

Pulmonary fibrosis in sarcoidosis

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Abstract. Sarcoidosis may progress to pulmonary fibrosis in 5% of patients with significantly increased mortality. Histopathology shows fibrosis in a lymphangitic pattern surrounding the granulomas. Th1 to Th2 shift in environment along with angiogenesis is implicated in exuberant fibrosis. Clinical features include dyspnea, cough, and frequently with pulmonary function tests showing a mixed ventilatory defect with severely decreased diffusion capacity of carbon monoxide. Serologic markers including soluble interleukin 2 receptor, chitotriosidase and kern von den lunges 6, and chemokine ligand 18 are elevated and implicated in progression of disease. CT imaging shows fibrosis along bronchovascular bundles with reticulations, traction bronchiectasis and honeycombing predominantly in the upper and central distribution. Complications include sarcoidosis-associated pulmonary hypertension (SAPH) and chronic pulmonary aspergillosis. Treatment involves glucocorticoids and steroid-sparing agents in the presence of active granulomas. Anti-fibrotic agents such as pirfenidone and nintedanib have been shown to slow down pulmonary function decline in randomized clinical trials involving sarcoidosis-associated pulmonary fibrosis. Transplant workup is indicated in New York Heart Association class III or IV with similar success rates as in other lung transplant patients.

Key words: sarcoidosis, pulmonary, fibrosis

Introduction

Pulmonary sarcoidosis can progress to fibrosis in roughly 5% of patients (3, 4). This subset of patients has higher morbidity and mortality that directly corresponds to the extent of fibrosis (2, 5, 6). This following review addresses the histopathology, genetics and clinical aspects of pulmonary fibrosis in sarcoidosis.

Histopathology

Non-caseating granulomas are the pathological hallmark of sarcoidosis that are present predominantly around the bronchovascular bundles, subpleural parenchyma and interlobular septa (7-9). A typical sarcoid granuloma exhibits core abundant in epithelioid cells, multinucleated giant cells and histiocytes with a surrounding rim of CD4+ lymphocytes as shown in figure 1 (8). The giant cells may display non-specific inclusions including asteroid bodies and Schaumann bodies (9).

Fibrosis in sarcoidosis follows distribution of granulomas in a lymphangitic pattern (7, 10). The predominance of fibroblasts and collagen in the periphery of granulomas supports the fact that fibrosis in sarcoidosis begins in the periphery and extends centrally into the granuloma (7, 9). Fibrosis may be restricted to small foci around granulomas or healed lesions or it may occur as an exaggerated fibrosis with frank destruction seen on histology and imaging. The latter phenotype has been regarded as sarcoidosis with pulmonary fibrosis (11).

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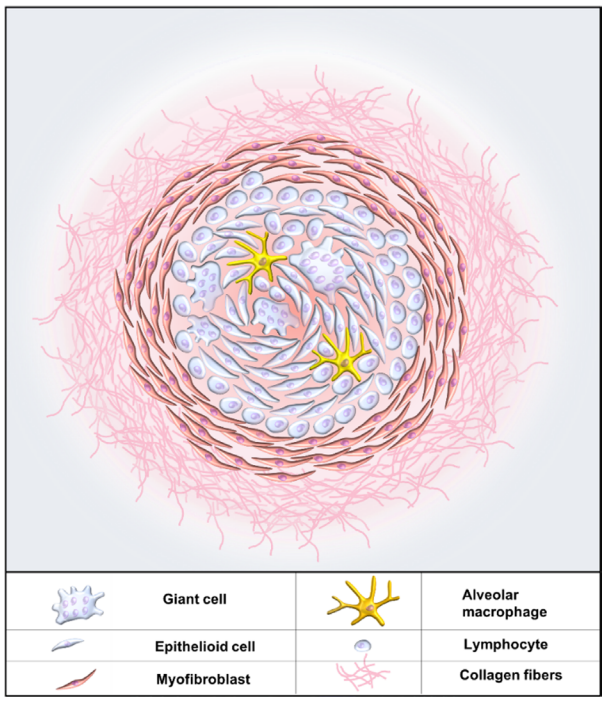

Fig.1. Non-caseating granuloma with surrounding myofibroblasts and dense collagen tissue in fibrotic disease in sarcoidosis.

Immuno-etiology

Active granuloma formation in sarcoidosis is largely driven by CD4+ T helper (Th)1,Th17.1, Th17, and T regulatory (T_{reg}) cells with evidence suggestive of environmental or microbial antigen presentation as a primary trigger (12-17). The antigenic presentation results in activation and differentiation of naïve T helper cells (Th0) into Th1, Th17, Th17.1 or T_{reg} cells (18). While Th1 and Th17.1 both produce IFN-γ, there is increasing evidence that most of IFN-γ, production is sourced from Th17.1 cells (19). IFN-γ is a Th1 prototype and activates macrophages that transform into epithelioid cells resulting in granuloma formation and tumor necrosis factor (TNF) production to maintain the granuloma (20).

Th phenotypes

The transition from early stages, with sarcoidosis granuloma to fibrotic disease is unclear. It is suggested that there might be a switch from Th1 to Th2 phenotype (21). Studies suggest, active sarcoidosis granuloma maintains Th1 response while also suppressing Th2 response (20, 22-24). For instance, IFN-γ mediates activation of Tbx2, a Th1 specific gene, in CD4+ cells. Tbx2 mediated expression of T-bet, a Th1 specific transcription factor, suppresses Gata3 (25, 26). Gata3 is a transcriptional factor that promotes Th2 differentiation as shown in figure 2 (27). IFN-γ also inhibits interleukin (IL) 4 (28), a Th2 committed cytokine.

Th2 phenotype is more conducive of fibroproliferation that is seen in fibrotic disease in sarcoidosis. Gata3 is implicated in exaggerated pulmonary fibrosis by promoting Th2 phenotype and production of IL10 and TGF-β from T_{reg} cells (27). Th2 cells produce IL 4 and IL13 that promote fibroproliferative state via enhanced TGF-β production [11]. The TGF-β induces differentiation of fibroblasts into myofibroblasts, the key effectors of fibrosis, that upon stimulation, cause collagen deposition, matrix production and contracture (25, 29-31). TGF-β also protect myofibroblasts against apoptosis prolonging progression of fibrosis (32).

It is unclear how the switch takes place from Th1 to Th2 phenotype. An imbalance in Th1/ Th2 regulation might be the trigger. In this regard, the role of a transcriptional factor, NRF2 in Th1/Th2 imbalance and subsequent fibrosis has been suggested (33). NRF2 deficient mice responded to bleomycin mediated fibrosis with exaggerated Th2 response and exuberant fibrosis. Further studies need to be done to explore expression of NRF2 in sarcoidosis with fibrosis. Analysis of cytokine profile in active granuloma versus overt fibrosis sarcoidosis will give a better insight into dominant phenotype and mechanism of pulmonary fibrosis.

Role of angiogenesis

Another vital component of fibrotic disease is exuberant angiogenesis that precedes and thus provides nidus for fibrosis. An imbalance in angiogenetic and angiostatic factors is suggested; chemokines and receptors that contain a three amino acid motif (Gleu-Leu-Arg) ELR, have been shown to have potent angiogenesis activity, such as IL 8, CXCL 2, CXCL 3, CXCL 4, CXCL 5 and CXCL 8 whereas those without the ligand show angiostatic activity, such as CXCL 10 and CXCL 11 (24, 34-38). Evidence shows increased angiostatic factors in Th1 environment while the angiogenetic factors are increased in Th2 environment promoting fibrosis as shown in table 1 (37, 39).

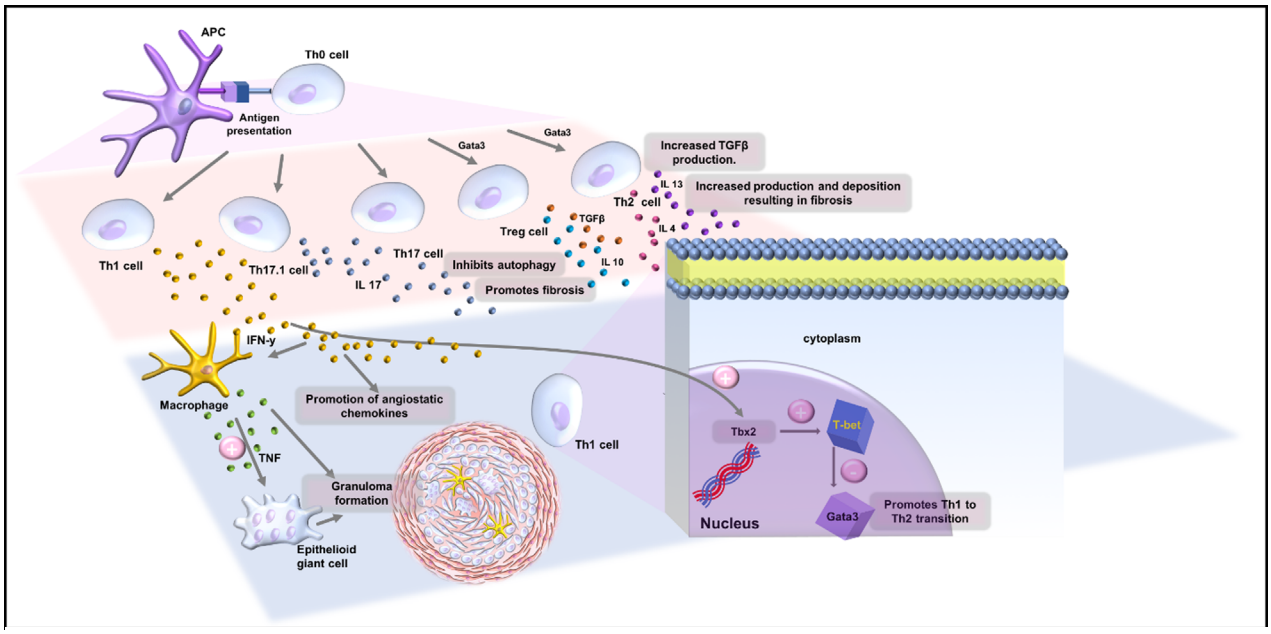

Fig. 2. Antigen presentation via antigen presenting cells (APC) activates Th0 helper cells that in the presence of specific cytokines, differentiates into Th1, Th17.1, Th17 or T_{reg} cells. IFN-γ activates macrophages that secrete tumor necrosis factor TNF and subsequently transition to epithelioid giant cells. IFN-γ mediates activation of Tbx2 gene activates transcription factor (TF) Tbet that inhibits TF Gata3. Gata3 is implicated in activation of T_{reg} cells to produce IL 10 and TGF-β and activation of Th2 cells that produce IL4 and IL 13 with downstream activation of collagen production and fibrosis.

Table 1. Chemokines and receptors involved in angiogenesis

Angiogenesis in fibrotic sarcoidosis			
Ligand	**Effect on angiogenesis**	**Levels in fibrotic disease**	**Reference**
CXCL 4	Inhibits	Decreased	(24)
CXCL 10	Inhibits	Decreased	(24, 35, 37)
CXCL 11	Inhibits	Decreased	(24, 37, 38)
CXCL 2	promotes	Elevated	(24, 35, 37)
CXCL 3	promotes	Elevated	(24, 35, 37)
CXCL 5	Promotes	Elevated	(34, 37)
CXCL 8	Promotes	Elevated	(34, 37)

Macrophage phenotypes

Macrophages are the prime structural blocks in a sarcoidosis granuloma. Like the CD4+ helper T cells, macrophages also have the ability to polarize; the classical form, M1, is activated in the presence of Th1 committed cytokines such as IFN-γ and TNF with resultant granuloma formation. On the other hand, the alternative form, M2 is activated in the presence of Th2 committed cytokines such as IL4 and IL13 and drives the responses of tissue remodeling, wound healing and fibrosis (40). M2 macrophages can be further classified into M2a, M2b, M2c, and M2d (41). M2a mediates anti-inflammatory responses, M2b cells are involved in persistent activation of M2 pathway and inflammatory responses, M2c contributes to tissue remodeling while M2d is involved in angiogenesis and tumor progression (42). The role of these M2 subtypes in sarcoidosis and fibrosis is an area of active research.

One of the pathways of M2 driven fibrosis is by production of the chemokine CCL18 (43). Prasse *et al.* showed that in the presence of Th2 committed cytokines IL4, IL 10 and IL 13, collagen stimulates CCL18 production by M2 macrophages via scavenger receptors (markers CD36 and CD 163) and

β_2-integrin receptors (marker CD 18). CCL18 in turn further augments collagen production by fibroblasts (43). This positive feedback loop is implicated in pulmonary fibrosis as shown in figure 3.

Gene expression

A strong genetic component is suggested in development of sarcoidosis with 80-fold increased risk of developing sarcoidosis in co-twin siblings of affected monozygotic patients (44). Certain genotypes and single nucleotide polymorphisms (SNP's) are associated with worse phenotype in sarcoidosis (45) as shown in table 2.

Clinical features

Pulmonary fibrosis in sarcoidosis may have a myriad of clinical presentations on a spectrum from asymptomatic at one end to respiratory failure on the other (46). Clinical presentation may include cough, wheezing, hemoptysis, clubbing, and crackles (2). Crackles is a relatively infrequent presentation compared to other pulmonary fibrotic diseases (47, 48). The presence of productive cough may suggest bronchiectasis and hemoptysis may indicate the need to rule out aspergillus infection (48).

Pulmonary fibrosis in sarcoidosis most frequently presents as mixed obstructive and restrictive ventilatory defect on pulmonary function tests (PFT's) as evident by both ratio of forced expiratory velocity in one second over forced vital capacity (FEV1/ FVC) and total lung capacity less than lower limit of normal of reference population (49). The interstitial fibrosis reduces lung volumes manifesting as restriction while the airway traction and stenosis presents as an obstructive defect (50) Evidence suggests higher mortality associated with mixed and restrictive ventilatory defects as compared to obstructive defects (49). Amongst PFT's, DLCO is the only

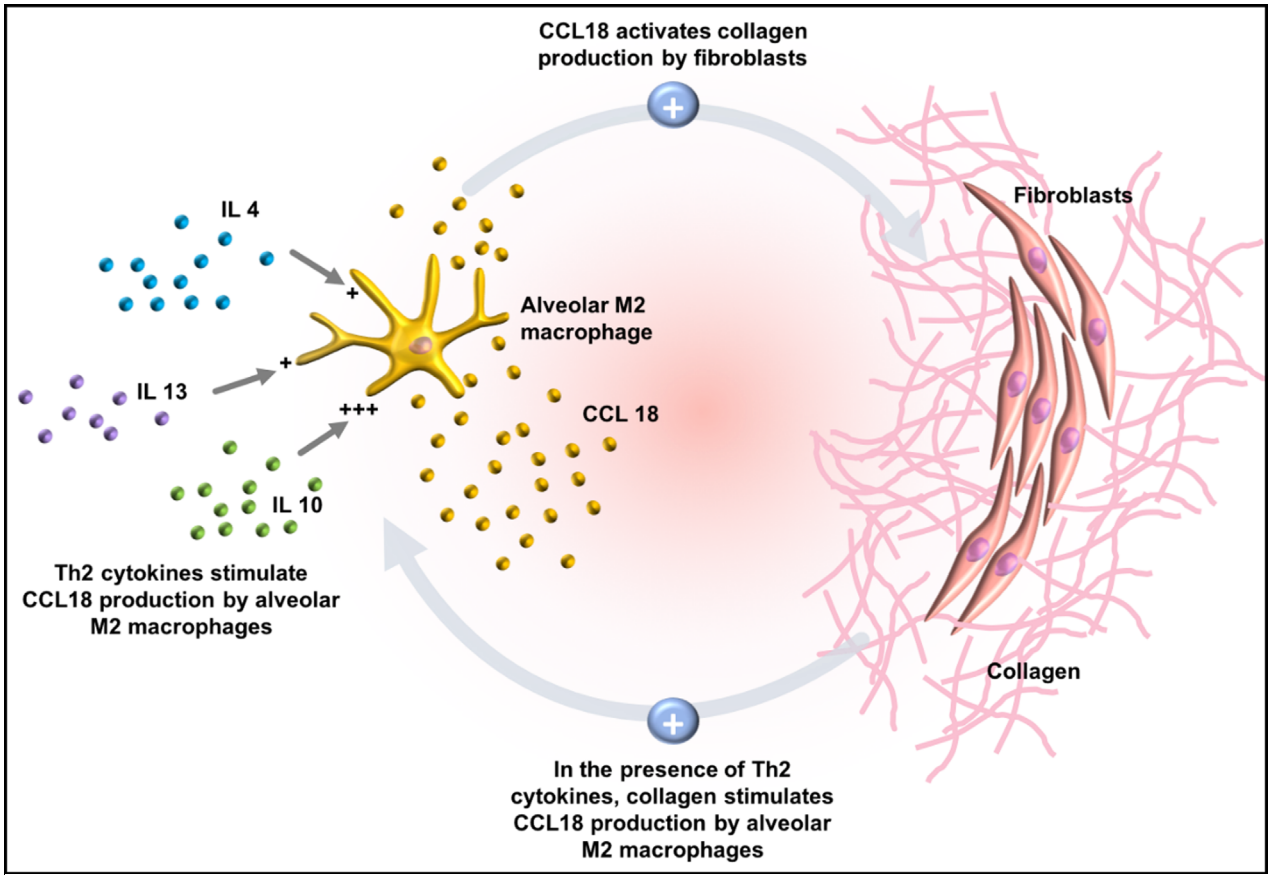

Fig. 3. Th2 cytokines mediated stimulation of M2 macrophages by collagen to produce CCL18. CCL18 in turn stimulates collagen production by fibroblasts starting a positive feedback loop leading to pulmonary fibrosis.

Table 2. Levels of genes and associated single nucleotide polymorphisms (SNP's) and alleles in sarcoidosis with fibrosis

Gene	SNP/Allele	Levels in fibrotic sarcoidosis	References
TGF-β3	TGF-β3 4875 A allele	Increased	(126, 127)
TGF-β3	TGF-β3 17369 C allele	Increased	(126, 127)
TGF-β3	TGF-β3 (rs3917200)	Increased	(126, 127)
HLA-DQBI	HLA-DQBI*0602	Increased	(128)
FCGR-2A	FCGR-2A- 131HH	Increased	(129)
FCGR-2A	FCGR-2A-131RH	Decreased	(129)
CARD 15,	CARD 15, 2104T	Increased	(45)
CCR5	Combination of CARD 15, 2104T and CCR5 HHC	Increased	(33)
BTNL2	BTNL2 G16071A	Increased	(25, 130).
Annexin 11	T frequency rs1049550	Increased	(131, 132).
Annexin 11	C frequency for rs127799558	Increased	(131, 132).

independent predictor of mortality in sarcoidosis and is a very sensitive function of alveolar loss (49, 51).

Serologic markers

Serum angiotensin converting enzyme (SACE) is a biomarker secreted by macrophages and is involved in granuloma formation (52, 53). Even though it may be elevated in sarcoidosis, there is low certainty regarding its diagnostic value with a low sensitivity and specificity (54). Evidence suggests it does not correlate to staging or progression to fibrotic disease (52). CD4+ cells are markedly increased in bronchioalveolar lavage of sarcoidosis patients, however these cells are reported to be low in BAL of patient with sarcoidosis with fibrosis (19).

In the past two decades, several other markers have been studied. Most noteworthy among these are soluble IL 2 receptor (sIL 2R), chitotriosidase, and kreb von den lungen-6 (KL6).

sIL 2R, also known as CD 25, is expressed in abundance by activated Th1 cells and acts as a receptor for IL 2 (55). IL 2 is produced by activated Th1 cells and involved in further proliferation of T cells. sIL 2R is therefore a surrogate marker of Th1 activity (56). Studies showed sIL 2R has a higher sensitivity and specificity respectively, compared to SACE in diagnosis of sarcoidosis and high levels is a prognostic marker for disease progression (56, 57).

Chitotriosidase is secreted by macrophages and unlike SACE, has high sensitivity and low specificity (52, 53). Interestingly, in a study including 228 patients, chitotriosidase levels were significantly elevated in patients with CT evidence of fibrosis (666.3 ± 311 nmol/ml/h) as compared to those with parenchymal involvement without fibrosis (284.2 ± 355.2 nmol/ml/h, p< 0.01) (58). Enyedi *et al.* suggest using the product of chitotriosidase and SACE, termed as the double product, instead of individual values to achieve higher sensitivity and specificity for diagnostic accuracy of sarcoidosis (AUC = 0.898, sensitivity: 90.5%, specificity: 79.3%, positive and negative predictive values: 90.5% and 79.3%, respectively) (53). However, their study did not include patients with fibrotic disease making its applicability questionable in these patients. Further investigation on identification of the macrophage subclass producing chitotriosidase will refine diagnostic role in fibrotic disease in sarcoidosis.

KL-6 is another serologic marker derived from alveolar epithelium and implicated in fibrogenesis with levels increased in interstitial lung disease (ILD) and IgG4-related lung disease(IgG-RLD) (52, 59-61). Bergantini *et al.* found a significant correlation between KL-6 levels and stage of sarcoidosis with highest levels noted in fibrotic disease (p<0.01) (60). Nonetheless, it is suggested for prognosis only, with not much diagnostic value, as levels are increased in many ILDs (61).

CCL-18, is also a serologic marker for IgG4-RLD, idiopathic pulmonary fibrosis (IPF) and systemic sclerosis (59, 62). CCL-18 is produced by antigen presenting cells and is implicated in Th2 response, M2 polarization, collagen production and fibrogenesis as shown in figure (62, 63). There is evidence of decline in CCL-18 levels after treatment in

IPF and system sclerosis highlighting its prognostic value (62). Further research is needed on CCL-18 as a therapeutic target beside its prognostic utility in fibrotic disease of sarcoidosis.

A recent study analyzed the plasma metabolic profile of African American sarcoidosis patients (64). Significant differences in levels of collagen pathway metabolites were seen, including p-coumaroyl-agmatine and palmitoyl-carnitine, between sarcoidosis patients with and without fibrosis ($p = 0.001$). Further research into these metabolites of collagen can increase accuracy in diagnosis of sarcoidosis with fibrosis.

Radiographic features

Chest radiographs are usually the first imaging to suggest diagnosis (65, 66). The most well-known staging system, proposed by Karl Wurm and revised by Guy Scadding in 1961, uses chest radiographs finding to stratify patients into 5 categories, stage 0-IV, based on the probability of resolution in 5 years (67). Fibrosis may include architectural distortion and volume loss in the upper zones on radiographs.

High resolution CT scan is a much more sensitive modality to assess parenchymal abnormalities and differentiate between fibrosis and inflammation (68).

The presence of micronodules, ground-glass opacities, and septal thickening may represent reversible parenchymal abnormalities suggestive of active granulomatous inflammation (69) and prompt reversal with treatment. On the other hand, architectural distortion, traction bronchiectasis, honeycombing and volume loss suggest irreversible fibrosis (70).

Micronodules, distributed in upper and mid lobes with peri-lymphatic distribution, are the most frequently identified CT finding seen in 70-90% sarcoidosis patients, however the incidence decreases to 25% with presence of fibrosis (68, 71).

Abehsra *et al*. suggested three major CT scan patterns in sarcoidosis with fibrosis; bronchial distortion, honeycombing and linear fibrosis (71). Bronchial distortion is the most frequently identified pattern seen in ~ 47% cases (71-76). It is usually distributed centrally, predominantly in the upper and middle lobes, and includes patterns of bronchial angulation, stenosis and broncho-vascular thickening. The bronchial distortion may accompany conglomerate masses in 60% of the cases with masses more than 3 cm surrounding the distorted bronchi (68, 71). These conglomerate masses may shrink overtime giving rise to bronchial distortion (77). (68, 71).

Honeycombing is the second major pattern observed in 29% of cases (71). Honeycombing in sarcoidosis is predominantly macrocystic with diameter ranging between 0.3- 2.5 cm (78). It is distributed in subpleural and upper zones and is associated with significantly decreased lung volumes and DLCO with increased oxygen requirements (71, 79).

Linear fibrotic pattern is the third major pattern seen in 24% of cases (71). This pattern shows a diffuse distribution and includes hilar peripheral lines, distorted septal reticulation and interlobular and irregular lines with a thickness between 1-3mm (71). While studies suggest that the linear fibrotic pattern is frequently irreversible (74, 75), it causes only slight functional impairment.

The modified Walsh algorithm incorporates the effect of disease via spirometry, extent of disease via HRCT findings and the extent of vasculopathy via MPAD/BSA ratio into one staging system that stratify patients based on prognosis mortality (6, 80). Evidence suggests this algorithm is an independent predictor of mortality (6, 80).

^{18}F-FDG PET scan is a very sensitive modality to identify active inflammation in sarcoidosis (81, 82). Granulomas appear as foci with increased SUV_{max}, although the pattern of ^{18}F-FDG uptake is non-specific (81). Fibrosis can be identified as abnormal confluent masses with ^{18}F-FDG uptake less than that of blood pool (83, 84). In sarcoidosis with fibrosis, ^{18}F-FDG PET/ CT may be beneficial to identify any occult inflammation and active granulomas. More research is needed before widespread use of FDG-PET/CT in fibrotic sarcoidosis.

Prognosis and mortality

Sarcoidosis with pulmonary fibrosis, that correlates with radiographic stage IV, is associated with worse survival rate as compared to stage 0-III disease, as well as the general population (HR 3.6, 95% CI 2.9–4.3; $p = 0.013$) (2, 5). The overall mortality in this cohort is also much higher ranging between 11-16% as compared to 2- 5% mortality in sarcoidosis patients in general (2, 5, 85). Furthermore, those with >20% fibrosis on HRCT have a higher 5 and 10 year mortality as compared to those with <20% fibrosis (18.18% vs 7.35%, HR=2.80, CI= 1.19-6.56,

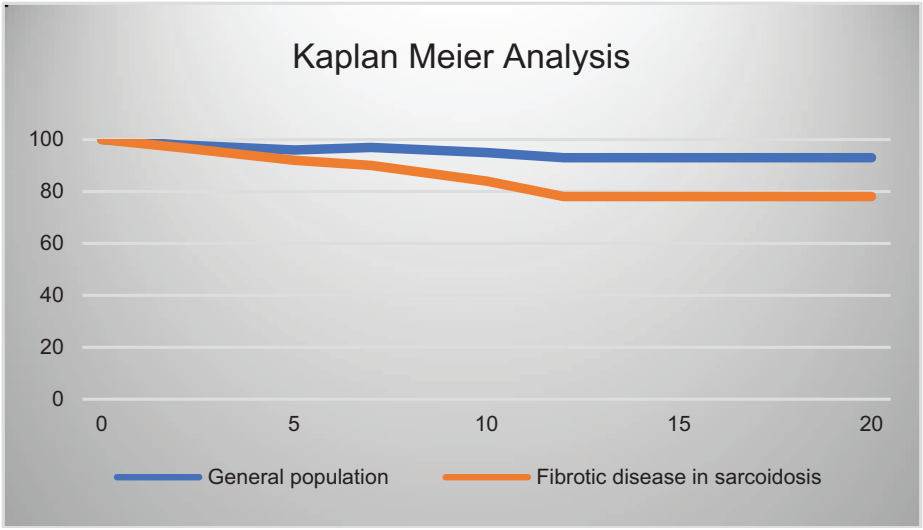

Fig. 4. Kaplan Meier Survival analysis for sarcoidosis with fibrosis as compared to general population. Figure reproduced with permission from European Respiratory Journal (2).

p=0.0178) (5). Figure 4 demonstrates comparison of survival in percentage in this cohort with general population. The average age at death in sarcoidosis with fibrosis is 55.2 ±12.3 years in the French population (2). Racially, the mortality follows the pattern of disease prevalence; African American are most affected at a younger age and also die at a younger age as compared to caucasians (51.8 ± 2.3 year vs. 65.2 ± 1 year; P < 0.0001) (86, 87).

In unclassified sarcoidosis patients, the three independent predictors of mortality are age (p=0.0093), >20% fibrosis on HRCT (p=0.0255) and SAPH (p=0.0484) (5).

Sarcoidosis associated pulmonary hypertension

The prevalence of SAPH is estimated to be 2.5-6.4% (5, 88). Pulmonary hypertension (PH) is an independent predictor of mortality in sarcoidosis with fibrosis (HR= 8.96, CI= 3.85-20.87, p= 0.048) (5), and a direct cause of mortality in about a third of fatalities (2).

Clinical presentation including exertional dyspnea, with >20% decrease or <300m distance in 6 minute walk distance (6MWD), worsening oxygen saturation >5% or >15% drop in DLCO without significant change in PFTs should prompt echocardiography (11, 89, 90). A peak tricuspid regurgitation velocity of >3.4ms^{-1}, or a >2.8 ms^{-1} and <3.4 ms^{-1} with echocardiographic evidence of PH, suggests high pretest probability for PH and a right heart catheterization should be performed (91, 92). Mean pulmonary artery pressure of >20 mmHg is diagnostic of PH with pulmonary vascular resistance of ≥3 Woods unit and a pulmonary capillary wedge pressure of ≤15 mmHg indicating pre-capillary PH. Amongst the treatment options, prostenoids, endothelin antagonists and phosphodiesterase inhibitors have shown to improve hemodynamics but without much change in 6MWD (93-96). Cyclic guanylate monophosphate inhibitor riociguat has shown to decrease time until clinical worsening in this subset of patients (97).

Chronic pulmonary aspergillosis

Chronic Pulmonary Aspergillosis (CPA) affects 2.6% of sarcoidosis patients, half of which have pulmonary fibrosis (98). Amongst sarcoidosis patients with fibrosis, 11% may develop CPA (2). Figure 5 demonstrates survival in percentage in patients with sarcoidosis with CPA. About 50% of CPA cases in sarcoidosis present as the chronic cavitary pulmonary aspergillosis (CCPA) phenotype, marked by cavitary lesions in the lungs with or without a fungal ball, known as aspergilloma (99). Aspergilloma is the second most common presentation seen in around 30% of CPA cases in sarcoidosis (99). The less common phenotypes include aspergillus nodules seen in 11%

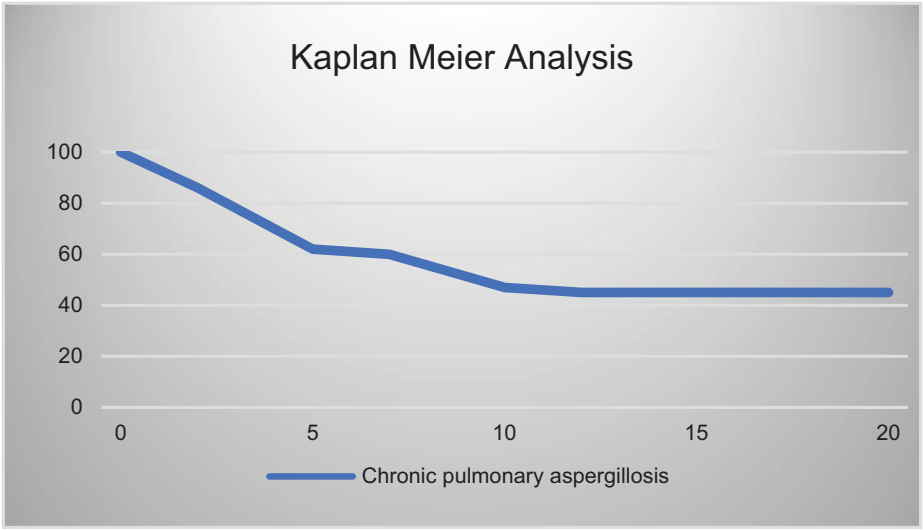

Fig. 5. Kaplan Meier Survival analysis for sarcoidosis patients with chronic pulmonary aspergillosis. Figure reproduced with permission from European Respiratory Journal (1).

and chronic fibrotic pulmonary aspergillosis seen in 15% of CPA cases (99).

CPA usually presents with non-specific symptoms of chronic cough, dyspnea, weight loss, and hemoptysis (1). Aspergilloma can be diagnosed with imaging, whereas, in CCPA the diagnosis can be challenging due to similar radiologic findings of cavitation seen in fibrosis in sarcoidosis (99). In the presence of clinical findings, CCPA can be diagnosed with imaging and positive smear and cultures for aspergillus(11). Serologically, Aspergillus IgG is more sensitive and specific (84.1% & 89.6%) than bronchoalveolar lavage fluid Galactomannan levels (79.1% & 84.2%) or serum Galactomannan levels (23% & 85%) (100).

Aspergilloma demonstrates poor response to systemic anti-fungal treatment due to its limited access to bloodstream (99). A CT-guided instillation of liposomal amphotericin is effective in patients that are poor surgical candidates for resection (101). Hemoptysis is treated with bronchial artery embolization (11) although relapse rate is very high (98). In sarcoidosis with fibrosis and cavitation, screening with levels of Aspergillus IgG, earlier detection and treatment may prevent progression to complications (98).

Treatment

In the presence of active granulomatous inflammation, glucocorticoids are the mainstay of treatment (102, 103). In case of inadequate response treatment can be escalated in a stepwise manner to steroid-sparing agents, including, methotrexate, and biologic including adalimumab and infliximab. (102-105). Given the side effect profile of current pharmacological option in sarcoidosis, there is rising interest in alternate therapies that are already approved for other conditions (106). A recent pilot study aimed to explore role of nicotine in sarcoidosis based on previous evidence of lower prevalence of sarcoidosis in active smokers (106-108). However, the role of nicotine in sarcoidosis with fibrosis has not been studied. In fact, smokers have higher incidence of interstitial lung diseases attributed to angiogenic effects of nicotine in addition to its role in induction of fibroblasts (109, 110).

The efficacy of anti-fibrotic agents in sarcoidosis with fibrosis is an area of ongoing research (111). Pirfenidone is one of the antifibrotic agents that has shown to decrease lung function decline in patients with idiopathic pulmonary fibrosis (112, 113). Its efficacy in sarcoidosis with fibrosis is currently being studied in a clinical trial (114). Nintedanib is another antifibrotic agent investigated for efficacy in chronic fibrosing ILDs. Patients were followed for 52 wks on Nintedanib vs placebo. Nintedanib use was associated with reduced ILD progression, measured with decline in FVC >10% predicted, (HR 0.66 [95% CI: 0.53, 0.83]; p=0.0003 (115, 116). These results are promising for its use to reduce progression of disease

in sarcoidosis with fibrosis. More research into effects of antifibrotics in fibrosis associated with sarcoidosis with fibrosis is needed.

Recently the role of roflumilast was studied in sarcoidosis with fibrosis (117). Roflumilast is a phosphodiesterase-4 inhibitor with established efficacy in reducing exacerbations in severe chronic obstruction pulmonary disease. (118). After a 12-month therapy, there was a significant improvement as demonstrated by decreased office visits where FEV1 was less than 90% of best FEV1 (OR =0.34 (CI 0.16 to 0.76 95%, p=0.0073) (117).

Transplant

Sarcoidosis patients constitute 2.5% of lung transplant recipients as compared to 31% IPF patients (119). According to data from national statistics from the US of admissions and death based on classification of diseases, ninth edition codes from 2009, for every patient of IPF <64 years age, admitted to hospital, 7 patients with sarcoidosis are admitted to hospital, whereas there are 6 inpatient deaths in IPF patients for every death in Sarcoidosis patients. However, the lung transplant ratio for IPF and sarcoidosis is 12:1, indicating underrepresentation of sarcoidosis patient receiving lung transplant (119, 120). While on the waitlist the mortality rate in the patients is as high as 53% (121). In a study with 43 patients on waitlist, multivariate analysis showed a right atrium pressure of >15mmHg as an independent predictor of mortality while on waitlist with a fivefold increased risk of death (121).

Due to the unpredictability and variable nature of the disease, there is paucity of data on optimal timing to list sarcoidosis patients for a lung transplant. The international society for heart and lung transplant consensus guidelines recommends referral for transplant evaluation in patients with New York heart association class 3 and 4 symptoms. Additionally, hypoxemia at rest, pulmonary hypertension, and right atrial pressures >15mmHg are indications for listing for transplant (122).

Among the commonly encountered presentations in sarcoidosis with fibrosis, bronchiectasis is an indication for a bilateral transplant to prevent infection from colonized native lungs (123). The presence of mycetoma is a relative contraindication due to the risk of seeding in the thoracic cavity and complicated explant in the presence of a thickened pleura increasing the risk of graft dysfunction (124). The post-transplant survival rates are similar to those seen in unclassified lung transplants (125).

Conclusion

The presence of pulmonary fibrosis in sarcoidosis significantly increases morbidity and mortality in these patients with high risk of progression to complications including pulmonary hypertension. The treatment of pulmonary fibrosis in sarcoidosis is an area of evolving research. Antifibrotics with known efficacy for fibrotic ILDs is the mainstay of treatment. Any active inflammatory component can be treated in a stepwise approach with steroids, steroid-sparing agents or biologics. Frequent clinical surveillance and follow up is crucial to early diagnosis of complications including PH and CPA and timely initiation of treatment.

Conflict of Interest: Each author declares that he or she has no commercial associations that might pose a conflict of interest in connection with the submitted article.

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