Rheumatology : Current Research

Review Article　　　　　　　　　　　　　　　　　　　　　　　　**Open Access**

Interstitial Lung Disease in Systemic Sclerosis: Diagnosis and Management

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In 460 B.C., Hippocrates described a syndrome of thickened skin. It wasn't until 1752 that this condition was described in more detail by Carlo Curzio. The term "scleroderma" was first used by Giovambattista Fantonetti in 1836. There was little interest in this disease again until the mid-late 1900's and now it is a clearly defined disease with ongoing research into pathophysiology and treatment options.

Scleroderma is broken down into three main categories: localized, systemic and sine. The first, localized sclerosis is limited to the skin. It has deep and extensive involvement of the skin but spares any internal organ involvement. Systemic Scleroderma (SSc) is divided into limited and diffuse based on the extent of skin involvement. Limited cutaneous (lcSSc) can involve the forearms, hands, legs, feet and face. Diffuse cutaneous (dcSSc) can involve any body area. Both will involve internal organs, differentiating them from the localized form. The last major category, Sine (ssSSc), is rare and involves only internal organs, sparing the skin.

Pulmonary Organ Involvement

Pulmonary disease is an important component of SSc. It is estimated that 80% of patients with SSc have some evidence of pulmonary disease. This makes pulmonary disease second only to esophageal disease as the most commonly seen visceral component. Moreover, pulmonary involvement portends a poorer prognosis. Pulmonary disease is now the leading cause of death amongst patients with SSc with an estimated mortality from pulmonary disease of all causes to be 33% [1]. While multiple pulmonary manifestations have been associated with SSc including pleural effusions [2], bronchiectasis [3], lung neoplasms [4], aspiration pneumonia and drug induced pneumonitis, the most common pulmonary manifestations of SSc include pulmonary hypertension and interstitial lung diseases (ILDs). The significant prevalence of ILD in SSc is reflected in the criteria of the diagnosis of SSc with the finding of predominantly basilar fibrosis being one of the three minor criteria utilized by the American College of Rheumatology for the diagnosis of SSc. This article reviews the specific manifestation of ILD in SSc.

Lung Fibrosis in Scleroderma

Like pulmonary fibrosis of most origins including idiopathic pulmonary fibrosis, the precise molecular events that occur in the pathogenesis of lung fibrosis is not well understood. The primary cytokines responsible for the disease are unknown but there is likely a complex interplay between inflammatory [5], B lymphocyte antibody production [6,7], oxidative stress and fibrotic pathways leading to the deposition of excess intracellular matrix. Lung fibroblasts play a central role as they are activated and produce extracellular matrix as well as many of the many of the inflammatory and fibrotic mediators [8]. This inflammatory response leads to fibrosis and occurs in the setting of vascular derangements [9].

It is unclear what environmental or genetic factors may contribute to the development of ILD in SSc. While environmental triggers have been considered in the pathophysiology of SSc in general and environmental exposures such as polyvinylchloride and an impurity in one preparation of L-tryptophan have been known to trigger scleroderma like syndromes, there has never been a clearly established environmental link. Moreover, there has never been an environmental

exposure implicated specific to ILD associated with SSc. Evidence suggests that gastroesophogeal reflux may contribute to the onset or progression of the disease, although the exact role of this reflux remains poorly understood [10,11].

A genetic contribution to scleroderma is supported by observed familial aggregation, ethnic predispositions, gene association studies and genome wide studies [12]. Pedigrees have been described that demonstrate members with SSC as well as members with ILDs not known to be related to SSc in numbers higher than would be expected by chance, suggesting a shared genetic predisposition between SSc, SSc ILD and non SSc ILD [13]. The heterogeneous nature of SSc complicates the interpretation of genetic studies and is a significant barrier to defining the genetic basis of SSc. Better characterization of phenotype may aid the understanding of scleroderma in general and the development of ILD specifically [12]. Genome wide profiling is a recent advance that has begun to tease out specific signatures that correlate with different manifestations of SSc. For example, activation of genes controlled by TGF-beta is seen more often in patients with interstitial lung disease [14]. This type of understanding will enhance studies of genetic factors related to SSc and will promote targeted therapeutic developments for different subtypes of scleroderma including those with ILD.

Subsets of Scleroderma Associated with ILD

The estimated prevalence of ILD in SSc ranges from 25-90% depending on the methods utilized and the subset of SSc patients evaluated [15]. There are currently no reliable means to consistently predict which scleroderma patients will develop ILD although African-American ethnicity, higher skin score and serum CPK levels, hypothyroidism and cardiac involvement have been reported to be associated with the presence of SSc ILD [16].

The association between SSC and ILD is strongest in patients who suffer from dcSSc although there is a well described association with lcSSC and ssSSc [17,18]. Patients with dcSSc typically develop the ILD early in the course of their disease. In the Registry of the Spanish Network for Systemic Sclerosis which included 916 patients with SSc, ILD was found in 70% of patients with dcSSc compared to patients with lcSSc or ssSSc in whom ILD was present approximately 39% of the time [17]. In this study, lung function was further characterized by SSc subgroup. Patients with lSSc appeared to have less severe ILD than those with dSSc with only 12% of the lSSc patients demonstrating a forced vital capacity (FVC) less than 70%. Although the incidence of ILD was similar in the ssSSc population and the lSSc population,

patients with ssSSc typically had worse lung function. The mean FVC in the lSSc population was 90.7% whereas mean FVC for the lSSc population was 83.1%. This suggests that careful screening should be done in all ILD patients to detect the presence of previously unsuspected SSc, particularly ssSSc.

Specific autoantibodies such as the anti-SCL-70, RNP, anti U11/U12 RNP, anti Th/To and antihistone antibodies have been reported to be associated with an increased risk of ILD in SSc [19] and others such as anticentromere antibodies are protective [17, 20]. However, because the antibody associations are neither specific nor sensitive [18], the efficacy of serologies as a clinical predictor of ILD is limited. These autoantibodies may ultimately prove to be markers of specific visceral involvement but a greater understanding of the significance of the autobody profile is needed. Further, the interplay of autoantibodies and the SSc subtype is not well understood. Gaining insight into these two clinical signals will enrich efforts to predict and treat SSc related ILD and is critical to an overall understanding of the heterogeneity of SSc [21].

Diagnosis of ILD in Ssc

The onset of ILD in scleroderma is often difficult to detect. Classically, patients with lung involvement will describe dyspnea with exertion as a first manifestation of disease. When examined closely, cough is a frequent and possibly underappreciated manifestation of ILD related to SSc. In the Scleroderma Lung Study, a multicenter trial enrolling only patients with confirmed SSc related ILD, 73% of the 158 participants reported the presence of a cough [22]. However, patients with mild disease may not report any symptoms referable to the pulmonary system.

Correctly identifying and managing ILD (with or without pulmonary hypertension) is a critical issue in the management of SSc. When studied systematically, approximately 50% of patients with ILD will demonstrate a measurable decline in pulmonary function within the first three years of diagnosis of SSc even amongst patients who report no pulmonary symptoms [23]. Therefore, early detection is important so that intervention can be considered prior to this rapid and early decline.

There are a number of tests that can be applied to the diagnosis of ILD in SSc. Physical examination can be revealing with the presence of bibasilar crackles, but often times these are subtle or absent early in the disease. A recent study from the Canadian Scleroderma Research Group found that findings of chest crackles on physical examination coupled with reticular markings on chest x-ray was predictive of SSc ILD with an likelihood ratio of 3.9 [24]. Often additional testing is utilized to detect or confirm the presence of ILD.

Pulmonary Function Testing

Pulmonary function testing (PFTs) is an important component of the evaluation of dyspnea and in the detection of pulmonary involvement in patients with SSc. Patients with significant interstitial lung disease will demonstrate restriction on lung function testing although normal pulmonary function may be present in mild disease.

Total Lung Capacity (TLC) by means of plethysmography is the most reliable measure of restriction and will confirm the presence of true lung restriction. However, spirometry is more typically utilized in clinical practice provides a good estimation of true restriction. Spirometry provides measures of the forced vital capacity (FVC) and the forced expiratory volume in one second (FEV1). In a restrictive lung disease, the FVC should be reduced and the FEV1/FVC ratio should be

normal. It has been estimated that 40% patients with scleroderma have a FVC of less than 75% predicted, marking the presence of ILD [25].

The diffusing capacity (DLCO) provides a measure of gas transfer between the air inhaled into the alveoli to the red blood cells in the systemic circulation. The DLCO is one of the most valuable measures in the evaluation of the scleroderma patient as a decreased value may be the earliest signal of lung disease in SSc and is reduced in 70% of SSc patients [26,27]. Moreover, the DLCO correlates most closely with the degree of disease seen on the high resolution computed tomography (HRCT) scan [28]. The DLCO will be reduced in both pulmonary hypertension and ILD. Thus, the DLCO is not specific for the diagnosis of SSc ILD.

The rate of decline of both the FVC and the DLCO are important prognosticators of survival [23,28]. The most rapid decline in the FVC occurs within the first three to five years of disease onset [23]. This implies that lung injury is an early event and suggests that frequent monitoring in lung function in early stage disease is important.

High Resolution CT

As with ILDs of all types, the HRCT is the most sensitive and specific modality for detecting and characterizing any ILD present in the setting of SSc. It is more sensitive than chest x-ray and is the imaging technique of choice [29]. The most common radiographic pattern is that of NSIP. Early in the disease, ground glass opacities are prominent in a peripheral distribution and then progress to reticular changes. The classic UIP pattern with bibasilar reticulation, traction bronchiectasis and honeycombing is also observed in patients with scleroderma but less commonly than NSIP. Honeycombing is seen more frequently in patients with limited SSc than in those with diffuse SSc [30]. A HRCT is required to make these radiographic distinctions.

The HRCT scan has limited prognostic significance. The finding of ground glass opacities does not universally connote reversible disease or alveolitis and is often fine reticulation below the threshold of CT detection [31]. The extent of ILD seen on HRCT does have prognostic significance. Patients who have more than 20% involvement of their lungs have increased mortality [32].

Bronchoalveolar Lavage (BAL)

The role of BAL in patients with SSc ILD is controversial and in evolution. When a cell count is done on BAL from patients with SSc associated ILD, elevated numbers of granulocytes may be seen, especially neutrophils and eosinophils. Increased numbers of lymphocytes and mast cells may also be seen [33]. Early studies correlated increased granulocytes in BAL with increased response to immunosuppression presumably because this represented active alveolitis [34,35]. Subsequently, BAL granulocytosis has been shown to correlate with the degree of ground glass opacity seen on HRCT [30] and with more advanced interstitial disease [36]. However, data from the Scleroderma Lung Study suggest that BAL granulocytosis does not add any additional prognostic information to HRCT and pulmonary function measures and is not a predictor of treatment response [36,37]. There is no question that BAL is an important test in the consideration of infection.

Biopsy

Similar to radiographic appearances, there are a variety of histologic subtypes found in SSc ILD. In one series, NSIP was the more common histopathology occurring in 76% of the cases [28]. In this same series, UIP occurred in 11% of the cases. There were also rare cases of

organizing pneumonia and diffuse alveolar damage. Importantly, the clinical outcome does not correlate with the observed histology [28,38]. Patients with scleroderma ILD can often experience stabilization after the initial development of their lung disease. In a series of 80 patients, survival does not differ between cellular NSIP, fibrotic NSIP and UIP. Thus, histology has no prognostic value. These patterns are in stark contrast to idiopathic ILDs where UIP is the most common pathology, the pathologic finding of UIP is associated with a poorer prognosis and stabilization of UIP for decades is rarely seen. Given this data, there is rarely value to a surgical biopsy in the evaluation of a patient with scleroderma associated ILD. The exception to this may be in cases of an unusual CT pattern which does not fit a predicted pattern seen in SSc.

Treatment of ILD in SSc

The decision of who requires treatment in the ILD associated with SSc is not straightforward. An effective therapeutic regimen should prevent progression to fibrosis. Therefore, treatments should target disease when a reversible component is present. Defining this reversible component can be difficult but new methodogies such as exhaled nitric oxide [39] and CT scan computer-aided diagnostic tools [40] and composite scoring systems [32] are being developed. In general, appropriate candidates for therapy are those who have early stage lung disease, have ground glass opacities on CT scan or who are demonstrating progression of disease.

Therapy of SSc will evolve as better understanding of the pathophysiology of scleroderma progresses. Similar to problems understanding genetic predisposition to SSc, a significant barrier to successful development of therapies is defining SSc subgroups. At present, therapeutic interventions are primarily immunosuppressant in nature although, increasingly, antifibrotic agents are also being investigated. While there are several drugs that have been evaluated in small series or with retrospective analyses, only a small number of drugs have been assessed via randomized controlled studies. Currently, few therapeutic options exist for patients with SSc ILD.

Cyclophosphamide

This drug has been the most rigorously assessed for use in SSc ILD. The Scleroderma Lung Study (SLS) [37] was a double-blind, 13 center trial of 158 patients with early SSc-associated ILD who demonstrated evidence of active alveolar inflammation with either ground glass opacities on HRCT or increased cellularity on BAL. Patients were randomized to receive either oral cyclophosphamide (≤2 mg/kg) or placebo daily for one year. In this study, the cyclophosphamide group had a smaller decline than the placebo group (-1.0 versus -2.6 percent predicted). This difference, while small, was statistically significant. This difference was seen at the end of the first year of treatment. In addition, a HRCT scan study was done on a subset of the SLS patients. With comparison of the initial CT scan and follow-up CT scan at one year, less progression of fibrosis was seen in the cyclophosphamide group [41]. Cough frequency also improved in patients treated with CYC for the 12 months of treatment and for 6 months after treatment, but this benefit disappeared at follow-up one year after stopping the CYC [22].

While these results suggest that cyclophosphamide is an effective, albeit with small impact, agent for treatment of SSc associated ILD, there are several additional considerations. There is significant toxicity associated with daily oral cytoxan including hematuria, cytopenias and malignancies. In addition, while there may be small improvements in lung function, quality of life may actually be worse for patients receiving oral cyclophosphamide [42]. Finally, there is concern that the response seen at one year is not persistent. While patient's reports of respiratory symptomatology and objective skin improvements were still present at the 24 month SLS follow-up study, the differential improvement in FVC had disappeared [43]. Interestingly, other groups have reported a durable impact of treatment therapy, with stabilization of lung function three years after intiation of cyclophosphamide prednisone combination therapy in patients with biopsy proven NSIP associated with scleroderma [44].

IV administration of cyclophosphamide is less rigorously studied but several uncontrolled studies [45-47] and one randomized trial has been done. In the 45 patient double blind placebo controlled study, there was a trend toward improved FVC in the cyclophosphamide group but this did not achieve statistical significance [48]. Thus, it remains unclear what the true role of IV cyclophophamide might be in the management of SSc related ILD.

Mycophenolate Mofetil

Mycophenolate (MMF) is an inhibitor of lymphocyte proliferation. In patients with rheumatoid arthritis, MMF has been reported to have antifibrotic effects [49]. In scleroderma ILD, MMF has primarily been the subject of retrospective studies and observational studies. In a prospective observational one year study of 14 patients who took MMF, 6 patients experienced at least a 10% improvement in their FVC and 5 patients' pulmonary function remained stable [50]. These small studies have had mixed results but, because observed improvements in FVC and DLCO have been documented [50-52], larger randomized trials are needed. This drug represents an attractive, less toxic possible alternative to cyclophosphamide. Importantly, MMF is currently being studied in the Scleroderma Lung Study II in direct comparison to cyclophosphamide.

Corticosteroids

The role of corticosteroids remains unclear in SSC related ILD. In general, these drugs are avoided because of the well known risk of scleroderma renal crisis. This phenomenon has been well documented [53] and has been reported to occur at mean doses as low as 7.4 mg [54]. However, in most clinical trials, use of prednisone was permitted with the drug under investigation. Thus, while monotherapy with glucocorticoids is not recommended, the role that the accompanying prednisone plays in combination with cyclophosphamide, mycophenolate or other therapies remains in question.

Other Therapies

There are a large number of other possible therapies that are under investigation. Beyond the consideration of inflammation as the primary driver of lung fibrosis, other pathways have been targets of study.

Endothelin receptor antagonists have been effective in the treatment of pulmonary hypertension associated with SSc. Bosentan for ILD was recently studied in a prospective, double-blind, randomized placebo-controlled, parallel group study. In the 163 patient study, the drug failed to demonstrate a difference in the primary endpoint of a change in six-minute walk distance. Secondary end points of time to death and worsening of PFTs were also no different [55]. This negative study mirrors negative results seen in trials of endothelin receptor antagonists in IPF [56].

Imatanib is a tyrosine kinase inhibitor that is an attractive agent because of the observed antifibrotic properties of tyrosine kinases inhibitors [57]. Specifically, infliximab has been shown to actually promote regression of fibrosis in a variety of fibrotic diseases including SSc [58]. In an open label trial of 24 patients, use of imatanib was

associated with a statistically significant improvement in FVC, although this effect was more pronounced in SSc patients without ILD. Imatanib is currently being further investigated for a possible role in SSc associated ILD and for SSc in general [59].

Rituximab is a monoclonal antibody directed against the CD20 antigen on the surface of B lymphocytes. Given that B lymphocytes are implicated in the pathogenesis of scleroderma, this drug also may have a role in the treatment of scleroderma lung disease. There have been small series reporting success in stabilizing lung function in patients with SSc ILD who failed to respond to cyclophophamide [60,61]. Again, large scale randomized studies are needed to verify the effectiveness of this drug for SSc ILD.

Stem cell transplant is under active investigation for the treatment of SSc. Given the putative role of B and T cells in this autoimmune disease, a stem cell transplant holds potential for cure by eradicating the culprit cells. While there has been reported success in improving skin thickening and stabilizing systemic disease [62], it remains to be seen whether stem cell transplant can improve outcomes in SSc ILD.

Lung Transplant

Lung transplant is an option for patients with SSc ILD when disease progression is not responsive to pharmacologic interventions. Once thought to be prohibitive because of an unacceptable mortality rate, lung transplant in SSc ILD has now been shown to have a similar prognosis for lung transplant for IPF [63-66]. However, these comparable survival rates require that the recipients are carefully selected. Factors that may be associated with a worse outcome include symptomatic gastroesophogeal reflux, delayed gastric emptying, recurrent aspiration, digital ulceration and renal failure [65,66].

Conclusion

ILD in SSc is a common manifestation that is associated with poor prognosis. Careful evaluation by the clinician is warranted to detect the presence of an ILD and to select patients appropriately for consideration of therapy. Early initiation of therapy should be particularly considered in patients with early disease, clinical progression and evidence of alveolitis. Possible side effects of therapy must be weighed against the known benefits. At the current time, cyclophosphamide remains the best studied therapeutic agent although alternatives are actively being evaluated. The pathogenesis of SSc-ILD and the heterogeneity of SSc are being actively researched and will advance our ability to care for these patients. Clinical trials are underway and offer hope for novel approaches to this mysterious and often devastating manifestation of SSc.

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