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Review

ILDs and CTD: a complex relationship

Stefano Sanduzzi Zamparelli[1,*], Alessandro Sanduzzi Zamparelli[2] and Marialuisa Bocchino[2]

[1]UOC Pneumology and Respiratory Physiopathology, A.O.R.N.A. Cardarelli, Naples, Italy;
[2]Department of Clinical Medicine and Surgery, Section of Respiratory Diseases,
University Federico II, Azienda Ospedaliera dei Colli-Monaldi Hospital, Naples, Italy.

ABSTRACT

Connective tissue diseases (CTDs) such as systemic sclerosis (SSc), rheumatoid arthritis (RA), Sjögren's syndrome (SS), idiopathic inflammatory myopathies (IIMs), systemic lupus erythematosus (SLE) and mixed connective tissue disease (MCTD), can be associated with a range of pulmonary manifestations including pleural involvement (pleuritis, pleural effusion, and pleural thickening), airways disease, vascular involvement (vasculitis), pulmonary hypertension, diffuse alveolar hemorrhage, and interstitial lung disease (ILD). In the course of systemic autoimmune disease ILD often appears early, representing even the first and/or the only manifestation. Up to 15% of the patients initially diagnosed with idiopathic nonspecific interstitial pneumonia (iNSIP) are found to have an underlying systemic rheumatic disease upon further investigation. Notably, ILD represents the leading cause of death in systemic autoimmune diseases patients, as marked in the EUSTAR database, being responsible for the death of 16.8% of SSc patients, followed by pulmonary arterial hypertension (PAH) (14.7%) and cancer (13.1%).

KEYWORDS: ILD, CTD, SSc, RA, SS, IIMs, SLE, MCTD.

INTRODUCTION

Among different autoimmune disorders, pulmonary fibrosis (PF) is particularly common in patients with SSc, as reported by literature, being evident on high resolution computed tomography (HRCT) in 64% or 43% of SSc patients, according to a Canadian or a Spanish study, respectively [1, 2]. This prevalence is so relevant that ILD was recently included by American and European association of Rheumatologists as a SSc diagnostic criterion in patients without a skin involvement (Table 1) [3].

Instead, ILD is a rarer occurrence in RA, as marked by a British data analysis showing that 6.2% of these patients (irrespective of signs/symptoms of ILD) shows pulmonary fibrosis on HRCT, although the onset is usually early, affecting 3.6% of patients with early RA (< 2 years of symptoms) [4]. It was estimated by a retrospective analysis that the lifetime risk of developing ILD is around 7.7%, compared with 0.9% in a matched cohort without RA [5]. The level of RA activity, measured using Disease Activity Score using 28 joints (DAS28), is linked to an increased risk of developing ILD, whit a surged risk of ILD by 35% for every unit increase in the DAS28 [6].

Although interstitial involvement shows up different radiological and pathological patterns in autoimmune disease-associated ILD, non-specific interstitial pneumonia (NSIP) pattern is more frequent in SSc-ILD, in SS and in IIMs such as polymyositis/ dermatomyositis; in contrast, the most common pattern seen in patients with RA-ILD is usual interstitial pneumonia (UIP) [7].

SSc

SSc is a chronic connective tissue disease, autoimmune, characterized by immune dysregulation, fibrosis of the skin and several organs, and vascular

*Corresponding author: stefanosanduzzi@gmail.com

Table 1. Lung involvement in CTDs.

Lung involvement in autoimmune disease				
CTD	**ILD occurrence**	**Predicting factor**	**ILD pattern**	**5-year survival rate**
SSc	Likely (40-50%) Diffuse cutaneous SSC (53%) Limited cutaneous SSC (35%)	Anti-topoisomerase ab (anti-Scl-70) Male gender African American race Diffuse skin involvement SP-D KL-6	NSIP (80-90%) UIP (10-20%) OP (rare)	90% (NSIP) 82% (UIP)
RA	Common (6-10%)	High RA activity (DAS28) MUC5B promoter variant Cigarette smoking Anti-cyclic citrullinated peptide ab (anti-CCP) Rheumatoid factor (RF) Male gender RA family history	UIP (40-60%) NSIP (30%) OP (8-11%) LIP or DIP (rare)	36% (UIP) 94% (NSIP)
SS	Possible (10-30%)	Female gender Older age Systemic manifestations (Raynaud's phenomenon and esophageal involvement) Hypergammaglobulinemia Anti-Ro (SSA), anti-La (SSB) and anti-nuclear ab Rheumatoid factor (RF)	NSIP (30-90%) UIP (16%) LIP (15-20%) OP (7-11%)	83% (NSIP)
IIMs (PM, DM, CADM)	Common (30-40%)	Acute/subacute forms Anti-ARS ab Anti-PL12, anti-PL7, anti-OJ, anti-KS ab Anti-MDA5 ab (only in DM and CADM)	NSIP (80%) COP (unusual) UIP (rare)	60-80% (PM/DM) 52% (acute/subacute forms) 87% (chronic form)
SLE	Unusual (3-10%)	Older age Long disease duration	NSIP (40-55%) LIP (9-30%) COP (unusual) UIP (rare)	93%
MCTD	Common (40-80%)	Long disease duration Systemic manifestation (dysphagia, esophageal dysmotility, Raynaud phenomenon) Anti-Ro52, anti-Sm and anti-U1-RNP ab Male gender Older age	NSIP (50-80%) UIP (rare) OP (rare)	> 95%

changes. It is a rare disease, with an estimated global prevalence of 3 to 24 per 100.000. Lung fibrosis occurs in up to 80% of patients with SSc, and 25% to 30% of patients develop progressive interstitial lung disease [8]. Literature underlines that pulmonary fibrosis is the leading cause of mortality, accounting for over 35% of SSc-related deaths. The course of SSc-associated ILD (SSc-ILD) is highly heterogenous, with a lung involvement that can be limited, stable or progressive [9].

The association between SSc and single nucleotide polymorphisms (SNPs) in the immune system genes, particularly interferon-regulatory factor 5 (IRF5), involved in activating interferon-activated genes, and the ligand of CD134 (OX40L), involved in antigen presentation and T and B cell activation is very intriguing [10].

SSc-ILD pathogenesis results from the interaction of epithelial, endothelial, and interstitial cells with the innate and adaptive immune system, after chronic and repetitive microinjuries in the lung. This fact leads to activation of the innate and adaptive immune system, recruitment of fibroblasts and differentiation to a myofibroblast phenotype, production of extracellular matrix (ECM) and fibrosis development. An epithelial-mesenchymal transition leads to profound morphological and biological cellular changes, such as loss of polarity, increased capacity for migration, increased production of ECM components, and increased resistance to apoptosis, a characteristic shared with myofibroblasts, contributing to the rate and extent of fibrosis in SSc-ILD. In this model, myofibroblasts seems to drive the profibrotic process, the persistence of which determines the pattern and type of fibrotic reaction. Interplay of myofibroblasts with the ECM *via* matricellular proteins, such as integrins and microfibrils, together with soluble factors, such as platelet-derived growth factor (PDGF) and connective tissue growth factor (CTGF), manages the fibrotic process, determining the progression or reversibility of the lung condition [11].

TGF-β (transforming growth factor-β), a believed key factor in fibrotic process because of its capacity to activate and differentiate fibroblasts, is implicated in ECM accumulation and regulation of immune response: its secretion from injured cells leads to immune cell chemo-taxes, including macrophages, major driver of TGF-β release. Increased expression of genes regulated by TGF-β has been confirmed in patients with progressive lung fibrosis. Increased thrombin levels, as a consequence of cellular injury in SSc-ILD, contribute to fibrosis by increasing proliferation of fibroblasts in response to fibrinogen and facilitating differentiation into myofibroblasts [12]. Elements involved in SSc pathogenesis, such as IL-6 and M2-like macrophages, may contribute to the lung involvement, especially in the early disease [13]. Increases in macrophage polarization, elevated C-reactive protein (CRP), and serum IL-6 levels have been associated with the progression of early SSc-ILD [14].

IL-4+ T cells and CCl18 levels in the BALF (bronchoalveolar lavage fluid) are associated with the severity of disease on HRCT imaging in SSc-ILD [15, 16]. Regarding adaptive immunity, in SSC-ILD, CD4+ CD25+ regulatory T cells and IL- 22–producing T-helper cells are increased in the lungs, benefitting from cyclosfamide treatment [17]. The major weight of adaptive immune mechanisms in SSc-ILD pathogenesis justifies the high prevalence of a good response to immunosuppressant therapy.

The development of fibrosis is a result of an initial ischemic process related to an endothelial injury: unlike in the early phase of SSc, wherein there is an increase in pro-angiogenic factors, in the late phase an anti-angiogenic and fibrosis response predominates. A potential trigger role may be attributed to circulating progenitor stem endothelial cells (PCs), which arise from a pool of circulating CD14+ cells. Indeed, due to their migration capacity, once PCs reach the site of injury, they may act as macrophages, fibroblasts and endothelial cells. In this way, these cells can exert inflammatory features, tissue remodeling properties and vascular modulation functions [18]. ILD is more frequent in patients with anti-topoisomerase autoantibodies and diffuse skin involvement [19]. SSc-ILD has been associated with a number of HLA-dependent genes and non-HLA genes, although only two variants confer an odds ratio of at least 2.0 with statistical significance: HLA- DRB1*3 (Han Chinese population) and CTGF rs6918698 (GG genotype; UK population) [20].

The most prevalent radiological and pathological pattern is NSIP, characterized by varying degrees

of inflammation and fibrosis, unlike the less frequent UIP pattern, with dense patchy fibrosis and honeycombing: those ILD patterns are responsible for a 90% and 82% 5-year survival rate and a 69% and 29% 10-year survival rate [21]. Pulmonary arterial hypertension (PAH) directly relates to vascular involvement (SSc-PAH), linked with the occlusion and remodeling of small pulmonary arterioles and, triggered by hypoxemia, can occur with or without the presence of ILD. The prevalence of SSc-PAH varies from 8–12% by right heart catheterization and up to 38% by echocardiography. Observational trials suggest that SSc patients with PAH and ILD have five times greater risk of mortality than those with SSc-PAH [22]. Compared with idiopathic pulmonary fibrosis (IPF), UIP pattern in SSc patients is characterized by higher numbers of lymphoid follicles, smaller honeycomb cysts, and fewer fibroblastic foci [23].

Epigenetic factors, called into question in the genesis, include CpG methylation, which is related to increased DNA methyltransferase expression in fibroblasts, affecting the activities of nitric oxide synthase or the collagen transcription suppression factor Friend leukemia virus integration 1 (Fli1), considered as a protective factor against ILD, upregulating the expression of genes, including autoimmune regulator and CXCL13 [24].

Four methylation-regulated genes (F2R, FYN, PAG1, and PRKCH) are underexpressed in SSc patients with interstitial involvement. In SSc-ILD patients the expression of the XRCC4 DNA repair gene is significantly increased. In animal models micro-RNA (miRNA)-increased expression (expecially miR-155) is associated with worsened lung function and increased lung fibrosis [25]. Risk factors associated with progressive ILD among SSC patients include diffuse cutaneous SSc, male sex, Afro-American race, and the presence of anti–Scl-70 antibodies (antitopoisomerase I antibodies or ATA) [26].

Although a huge number of blood serum or BALF biomarkers have been identified as potential indicators of lung involvement in SSc patients, only autoantibodies are currently available in routine clinical practice. The presence of anti–Scl-70 anti-bodies and the absence of anti-centromere antibodies in SSc indicate an increased likelihood of progressive ILD [27]. Among biomarkers under investigation, high KL-6 (Krebs von der Lungen-6) plasma levels appear to be linked to lung involvement and ILD progression in patients with SSc [28]. Serum CCL18 (chemokine [C-C motif] ligand-18), a macrophage 2–derived protein that is chemotactic for a number of immune cells, has also been shown to be a good prognostic marker, even after adjustment for baseline ILD severity [15]. Higher serum levels of matrix metalloproteinase-7 (MMP7), matrix metalloproteinase-12 (MMP12) and CCL2 are predictive of ILD progression and shorter survival. Data from literature marked that elevated acute-phase reactants such as CRP or IL-6, are associated with an increased likelihood of progressive early SSc-ILD [29]. CXCL4 (chemokine [C-X-C motif] ligand-4), a protein secreted by plasmacytoid dendritic cells, whose level in the BALF is associated with the severity of HRCT progression, correlates with the occurrence of ILD and with higher decline in diffusion lung carbonium oxide (DLCO) in SSc patients. A reduction in CXCL4 plasma levels due to immunosuppressive therapy over the first year of treatment is associated with greater improvements in lung function over the subsequent 12 months [30]. Serum levels of chitinase-3–like protein 1 (YKL-40) and chitinase 1 have been shown to be higher in patients with SSc ILD [31]. Although not routinely performed in SSc-ILD patients, proteomic BALF analysis identified the differential expression of a number of potential biomarkers including complement 3 anaphylatoxin (C3a), apolipoprotein A-I (APOAI), 14-3-3e, pulmonary surfactant–associated protein A2 (SPFA2), and S100 calcium-binding protein A6 (S100A6), involved in fibrosis, innate immune responses, and vascular damage [32].

Unlike other CTDs, SSc is the one on which more trials have been made about immunosuppressive therapy efficacy. Scleroderma Lung Study I (SLS I) was a 1-year, placebo-controlled trial that shows a 2.53% statistically significant improvement in forced vital capacity (FVC) due the use of Cyclophosphamide versus placebo ($p = 0.03$), in addition to positive effects on dyspnea, skin thickening, and quality of life [33]. SLS II, comparing 1 year of Cyclophosphamide with 2 years of mycophenolate mofetil, suggests that the two drugs are similarly efficacious after 24 months of treatment (mean FVC improvement of 2.88% and 2.19%, respectively), with fewer side

effects for mycophenolate mofetil (lower rates of leucopenia and thrombocytopenia) [34]. Data limited to SSc-ILD case series have shown the positive effect of rituximab in preventing FVC decline. Little is known about the role of low-dose of systemic glucocorticoids (prednisone 10-20 mg/day) in the management of SSc-ILD, avoiding high doses linked to acute renal failure [35]. A phase II study of imatinib at doses of up to 200 mg/day tested in 30 SSc patients with active ILD, shows improvement or stabilization of lung disease in 15% up to 58% [36]. Recently, on the basis of the results of Safety and Efficacy of Nintedanib in Systemic Sclerosis (SENSCIS) trial, nintedanib became the first U.S. Food and Drug Administration–approved treatment for SSc-ILD, slowing the rate of pulmonary function decline. SENSCIS trial showed that the adjusted annual rate of decline in FVC was 52.4 ml/yr in nintedanib-treated patients versus 93.3 ml/yr in placebo-treated patients (P = 0.04) over a 1-year period. Subsequent subgroup analyses reported that nintedanib reduced the progression of ILD irrespective of mycophenolate use at baseline [37]. The phase II LOTUSS (Safety and Tolerability of Pirfenidone in Participants with SSc-ILD) trial showed that pirfenidone administered either as monotherapy or in combination with mycophenolate mofetil had an acceptable tolerability profile in patients with SSc-ILD. SLS III, designed to compare pirfenidone plus mycophenolate mofetil with mycophenolate mofetil alone in SSc-ILD, showed a similar magnitude of improvement over 18 months in FVC% with a more rapid improvement over the first 6 months [38].

RA

RA is a systemic inflammatory disorder that affects an estimated 1% of the population in the USA and northern European countries. Among RA extra-articular manifestation, lung involvement is the most common, which can affect up to 60% of RA patients during the disease course. Though lung involvement in RA typically occurs following articular manifestations within the first 5 years of disease, occasionally respiratory symptoms may precede onset of articular symptoms in 10–20% of cases [39]. RA lung involvement can affect any compartment such as parenchyma (manifesting as ILD or rheumatoid nodules), pleura (resulting in pleural inflammation and/or effusions), small and large airways (cricoarytenoiditis, constrictive or follicular bronchiolitis and bronchiectasis) and pulmonary vasculature (vasculitis and pulmonary hypertension). Lung involvement, particularly RA-ILD, is associated with significant morbidity and mortality, accounting for death in 10-20% of patients. Unlike majority of CTDs, in which the most frequent ILD is NSIP, the most frequent subtype of RA- ILD is UIP, which has the worst prognosis: its prevalence valuated by HRCT ranges from 19% to 56% [40].

Studies on twins have explored genetic weight in RA, demonstrating concordance rates of 15-30% in monozygotic twins and 4% in dizygotic twins [41]. Genetic factors, mainly in the class II major histocompatibility complex (MHC) region, confer a risk of up to 50% for the development of RA: the most impacting is the human leukocyte antigen (HLA)-DRB1 allele, involved in adaptative immune response activation, by antigen presentation to T-cell [42]. HLA-B54, HLA-DQ1B*0601, HLA-B40, and the site encoding a-1 protease inhibitor are associated with an increased risk of RA-ILD [43]. A shared epitope in HLA-DRB chain, conserved aminoacid sequence, is highly associated with the presence of anti-cyclic citrullinated peptide antibodies (anti-CCP) and the development of RA [44]. Many variants were identified to be associated with increased susceptibility to pulmonary fibrosis, with similarities between RA-ILD and familial idiopathic pulmonary fibrosis (fIPF). The MUC5B promoter variant, the strongest genetic risk factor for IPF, which is involved in airway clearance and bacterial host defense, was observed in more than 50% of RA patients, being associated with UIP pattern [45]. An exome sequencing study found that patients with RA-ILD show an excess of mutations in genes such as TERT, RTEL1, PARN and SFTPC, previously linked to fIPF [46].

Among environmental risk factors, cigarette smoking seems to be a risk factor for development of seropositive RA, as well as RA-ILD: smoking is implicated in promoting lung protein citrullination by altering peptidylarginine deiminase function, changing lung self-proteins into autoimmune targets [47]. Onset of lung disease typically occurs in the fifth to sixth decade of life. Although RA is more common in females, RA-ILD occurs more

frequently in males, with a male to female ratio as high as 2:1 [48].

RA patients typically have circulating antibodies such as rheumatoid factor (RF) and anti-CCP in 50-80% of cases, that can often be detected several years before the clinical disease onset. This evidence suggests the antibody's role in the development of inflammatory response which leads to a clinical disease in a genetic predisposition condition [49]. Although anti-CCP autoantibodies are not very sensitive (20–30%), they are highly specific for RA-ILD (>95%) and in particular for UIP pattern [50]. Anti-CCP levels can be detected prior to the RA diagnosis: citrullinated versions of heat shock protein (Hsp) 90 isoforms a and b are autoantibody targets that distinguish RA patients with and without ILD, MCTD, and IPF [47]. A recent study has found that anti-CCP levels are increased in smokers and nonsmokers with RA-ILD in comparison with those without lung involvement. BALF in RA-ILD patients is often abnormal but nonspecific, with lymphocytosis more common in RA-ILD patients with a pattern other than UIP pattern, while neutrophilia is more common in patients with UIP pattern [51].

In murine models interleukin (IL)-17 plays a key role both in the pathogenesis of RA-ILD and IPF: TH17 cytokines, such as IL-17A and TGF-β, cause fibrosis through direct effects on fibroblasts, leading to their proliferation and extracellular matrix generation [52]. Different extra-pulmonary manifestations may be linked with immunogenetic factors such as the HLA-DR genes, that may lead to citrulline-target immune responses mediated by anti-CCP and possible articular disease [53].

Because of the absence of randomised controlled trials (RCTs), a definite RA-ILD treatment doesn't exist. Corticosteroids are the mainstay of therapy in RA-ILD, particularly for cases of NSIP where they may lead to clinical improvement. In one study of CTD-ILD patients (among which 11 RA-ILD patients including some with UIP pattern), the pulse-dose steroids therapy followed by 1 year combination therapy with tacrolimus brought to an improvement in FVC, and patient-reported symptoms [54]. Unlike SSc-ILD RCT, there are no studies examining mycophenolate mofetil efficacy specifically in RA-ILD patients: in a review of CTD-ILD patients (including RA-ILD patients), treatment with mycophenolate mofetil for a median of 897 days was associated with improvements in FVC % and DLCO % in non-UIP pattern patients and stabilization of lung function in those with UIP [34]. The humanized IL-6 receptor monoclonal antibody tocilizumab may modify the prognosis of ILD and other systemic manifestations of RA, but no RCT has yet been carried out.

SS

SS is the second most common autoimmune disease after RA, with an incidence between 3.9 and 5.3 cases per 100.000 person-years in Europe and a prevalence around 43 per 100.000 inhabitants (0.5%). There is a clear female prevalence, with a 9-13:1 F:M sex ratio and an advanced age preference, affecting mostly middle-aged women with a peak at 56 years of age [55].

Like other autoimmune diseases, SS shows a specific genetic background associated with environmental factors such as viruses (cytomegalovirus, HIV, HTLV and HCV) or solvents, and hormonal deregulation, which leads to an initial gland inflammation called autoimmune epithelitis and a deregulated immune response driven by B and T cells [56]. Impaired B-cell demethylation, activation and proliferation leads to plasma cell secretion of anti-Ro (SSA) and anti-La (SSB) autoantibodies directed to the small cytoplasmic RNP-bound peptides SSA-60kD, SSA-52kD and SSB-48kD [57]. It has been demonstrated in mice models that anti-Ro52 autoantibodies directly cause gland dysfunction [58]. Unclear is the role of T-cells, even if its activation has certain cytotoxicity effects. It is involved also in innate immunity, with a pro-inflammatory trend, probably based on interferon alteration, apoptotic cell clearance defect, interaction between P2X7 receptors and inflammasome. This immune response, combined with local inflammation, gland infiltration and anti-Ro52 autoantibodies, can lead to bronchopulmonary involvement, with sicca symptoms affecting up to 95% of patients, and extra-glandular symptoms, occurring in up to 1/3 of SS patients [59]. Notably, besides SS, anti-SSA60 autoantibodies are associated with SLE and foetal–maternal autoimmune syndromes, while anti-Ro/SSA52 autoantibodies are expressed in SLE (53%), myositis (35%), SSc (19%), primary biliary

cirrhosis (28%) and neonatal lupus in babies born from SSA antibodies positive mothers [60]. Many BALstudies found in more than half of SS patients (64%) a T-cell lymphocytic alveolitis, regardless of the presence of symptoms linked to a higher level of gammaglobulins, RF and anti-nuclear antibodies, justifying the higher mortality [61].

The prevalence of SS lung involvement such as airway abnormalities, interstitial pneumonia and lymphoproliferative disorders, is about 9-20%, even if imaging abnormalities are found in 34-50% of patients, without correlating with lung capacity or symptoms [62]. Subclinical lung disease is even more frequent, including small airway disease and inflammation. Systemic manifestations and autoantibody positivity such as anti-SSA, are predisposing ILD factors. Other risk factors associated with the onset of SS-ILD are older age, Raynaud's phenomenon, and esophageal involvement [63]. The annual incidence of respiratory manifestations is estimated at 10% (±3%) 1 year after diagnosis of SS and increases to 20% (±4%) by 5 years. Observed ILD prevalence in SS is about 3-11%, leading to fatal complications such as respiratory failure and secondary PAH, being responsible for 42.9-90% of the deaths. Although usually in 74.4% of cases, lung involvement is diagnosed after or at the same time as CTD, sometimes SS develops after clinical and radiological appearance of an ILD in 25.5% [64].

HRCT detects in 30–90% of SS patients, lung abnormalities consistent with NSIP pattern, such as ground-glass opacities, nonseptal linear opacities, interlobular septal thickening and multiple air cysts with tiny walls and random distribution, with honeycombing and fibrosis poorly represented [65]. Less frequent ILD patterns are UIP in 16%, organizing pneumonia (OP) in 7%, lymphoid interstitial pneumonia (LIP) in 15% and mixed in 17% of cases [66]. UIP more often affects the older and women, and it is associated with worse prognosis and progression despite therapy. LIP, considered as a benign lymphoproliferative disorder linked to follicular bronchiolitis, is characterized by diffuse proliferation of polyclonal lymphocytes and plasma cells in the pulmonary parenchymal interstitium, with lymphoid follicles and germinal centers [63]. Lung and airway involvement are often associated with centrilobular nodules present in 78% of cases of SS-ILD.

Although majority of SS patients have preserved lung functions, pulmonary function tests (PFT) reflect impairment of either the lung (restrictive syndrome) more frequently or airways (obstructive syndrome) [61]. As reported by Davidson *et al.* reduced DLCO is the most common abnormality in SS patients, in particular during first years of disease, remaining stable during follow-up [67]. Although SS-NSIP 5-year survival rate is 83%, the outcome is unpredictable, ranging from reversion with a risk of progression, stabilization with residual disease, irreversible progression with potential stabilization or irreversible despite therapy [68].

Usually, corticosteroids (ranging 0.5–1 mg/kg/day) in combination with immunosuppressive drugs (azathioprine or cyclophosphamide) represent the first line therapy [69]. Although a French review, analyzing 8 SS-ILD patients treated by rituximab, reported that 6 patients improved after beginning treatment with rituximab, a recent trial found a significant increase in adverse events (mainly respiratory infections) [70]. Recent evidences suggest the addition of immunosuppressive agents such as azathioprine, cyclosporine, infliximab, rituximab, and tocilizumab in refractory cases [71].

IIMs

IIMs are a various group of autoimmune diseases characterized by muscular involvement and extra-muscular manifestations, including skin and lungs. In addition to the 2 major subtypes of IIMs, polymyositis (PM) and dermatomyositis (DM), clinically amyopathic DM (CADM) is defined as the presence of a typical skin rash consistent with DM with minimal or no features of muscular manifestations [72].

In PM, DM, or CADM patients, lung involvement is present in 40% of cases. Notably, ILD is the most severe extra-muscular involvement in IIMs, whose presence is linked with a worse prognosis. Clinical courses and prognoses of PM-/DM-/CADM-ILD are heterogeneous: DM-ILD and CADM-ILD have poorer prognosis, due to refractory treatment, than PM-associated ILD [73]. Lung involvement can be distinguished in an acute/subacute form, defined as a progressive deterioration within 3 months, and a chronic form, defined as a slowly progressive and gradual deterioration over a period greater than 3 months.

Patients with acute/subacute forms of PM/DM/CADM-ILD had a worse survival than those with the chronic form (52% and 87% 5-year survival, respectively). The importance of the assessment of myositis-specific autoantibodies (MSAs), which are closely linked to clinical phenotypes of myositis-associated ILD, is emphasized in the literature. Although MSA positivity is present in approximately 80% of PM-/DM-/CADM-ILD patients, is not part of the diagnostic criteria: some types of MSAs such as the anti-aminoacyl tRNA synthetase (ARS) antibody and the anti-melanoma differentiation-associated gene 5 (MDA5) antibody are always present in PM-/DM-/CADM-ILD [72]. Among myositis-associated antibodies, anti-PM/Scl antibodies are mostly found in Caucasian patients with PM/SSc overlap syndrome, as well as in patients with PM or SSc, while they are very rare in patients with PM-/DM-/CADM-ILD [74]. Eight types of anti-ARS antibodies (Jo-1, PL-7, PL-12, EJ, OJ, KS, Zo, and Ha) were detected in 35-50% of PM-/DM-/CADM-ILD patients, in which antibody subtypes lead to unique features and prognoses. Although anti-ARS antibodies (anti-Jo-1, anti-Ej, anti-Oj, anti-PL-7 and anti-PL-12) are linked with similar clinical characteristics related to anti-synthetase syndrome (ASS) including myositis, ILD, polyarthritis, Raynaud's phenomenon, and mechanic's hands, anti-PL12 and anti-PL7 positivity is associated with severe ILD, whereas the presence of anti-Jo1 is related to frequent arthritis and muscle involvement [75]. Literature reports show up that PM-/DM-ILD patients with anti-ARS antibody-positive respond well to glucocorticoid treatments plus immunosuppressor achieving a 90% 5-year survival rate vs steroid therapy alone owing to ILD relapses [76]. Anti-MDA5 antibodies, previously named anti-CADM140 antibodies, were present in 30-50% of patients with DM with muscular involvement and in those with CADM, but not in PM patients, according to Asian studies: this antibody positivity is associated with a high incidence of ILD in DM/CADM patients, especially rapidly progressive form, and worse prognosis, being associated with 1-year survival rate of around 60-70%. The majority of fatal outcomes in anti-MDA5 antibody-positive DM-/CADM-ILD patients occurred within the first 6 months after the initial diagnosis. Because of high serum ferritin level, it is believed that macrophage activation involvement is linked with anti-MDA5 antibody-positive DM/CADM-ILD pathogenesis [77].

As in the case of most CTDs, IIMs-ILD may occur before, after, or at the same time as the development of extra-pulmonary manifestations. Risk factors for developing lung involvement include older age (>45 years), joint involvement, and ARS positivity [78]. In myositis-related ILD patients HRCT usually shows bilateral reticulations and ground-glass opacities, elements related to NSIP pattern (approximately 80%) and less frequent areas of consolidation pointing the presence of OP. The 5-year survival rate of PM/DM-ILD patients ranges from 60% to 80% [79].

Although guidelines doesn't exist for the management of IIMs-ILD, steroids in association (or not) with immunosuppressant agents (cyclophosphamide, AZA, mycophenolate mofetil, tacrolimus and cyclosporin A and rituximab) are considered to be the cornerstone of treatment for PM-/DM-/CADM-ILD. Recent studies have shown the efficacy of two members of calcineurin inhibitors (CNIs) that target T-cell activation, cyclosporin A and tacrolimus, in severe forms of PM-/DM-/CADM-ILD. Early intervention with Cyclosporine A plus steroid improves DM-/CADM-ILD prognosis with better disease stabilization and survival rate, as confirmed by Go *et al*. [80, 81]. Tacrolimus, a second-generation CNI with a 100-fold great potency for the inhibition of T-cell activation compared with cyclosporin A, is effective in PM-/DM-/CADM-ILD patients resistant to conventional treatment, as pointed out by Sharma *et al*. study, showing an improvement in myositis and ILD in 72% of PM-/DM-ILD patients who failed to conventional treatments [82]. A recent RCT, comparing the efficacy between steroid treatments plus tacrolimus or cyclosporin A in PM-/DM-/CADM-ILD patients, showed a 52 week progression-free survival rates of 87% and 71% in the tacrolimus and cyclosporin A regimens, respectively, with no difference in survival rate [83]. Azathioprine and mofetil mycophenolate, members of the family of antimetabolite drugs, are commonly used in ILD-IIMs as steroid sparing agents at a dose of 1–2 mg/kg and 2000–3000 mg/day, respectively [84]. Many studies highlighted the efficacy of rituximab, a chimeric anti-CD20

monoclonal antibody that targets and depleting B cells, in IIMs-ILD with anti-ARS antibody treatment, improving both PFT and HRCT images [85]. Literature demonstrated also the effectiveness of Rituximab in PM-/DM-/CADM-ILD patients with anti-MDA5 antibody positivity as a rescue therapy in the management of refractory cases [86]. Recent studies support the use of tofacitinib (10 mg/day), a Janus kinase inhibitor that blocks multiple signaling of cytokines such as interferon and IL-6, in anti-MDA5 antibody-positive DM-/CADM-ILD and anti-MDA5 antibody-positive ADM-ILD patients resistant to triple therapy, characterized by the overproduction of multiple cytokines [87]. The initial treatment should be determined by considering the severity of ILD (clinical symptoms, pulmonary functions, and chest HRCT findings) and factors associated with poor prognoses (mainly acute/subacute form, rapidly progressive ILD and anti-MDA5 antibody-positive in addition to old age, hypoxia, elevated ferritin, elevated KL-6, elevated CRP, and low FVC) [76]. Because of this poor prognosis, a combined steroid-immunosuppressive regimen, including CNIs and cyclophosphamide is recommended [88].

SLE

SLE is a systemic autoimmune disease with multisystemic involvement, including skin, joints, central nervous system and kidneys. SLE prevalence ranges from 40-200 per 100,000 of population, mainly affecting African and Asian ancestry and females, with a male to female ratio of 1:9. Among pulmonary involvement that can occur in SLE, such as pleuritis, pulmonary thromboembolism, diffuse alveolar hemorrhage, and shrinking lung syndrome, ILD is less common compared to other autoimmune disorders, affecting 3-10% of patients overall [89]. A contrasting report underlines a 29% ILD prevalence among SLE patients, half of which was present at the time of SLE diagnosis.

Similar to other CTDs, older age is a known risk factor for SLE-ILD, as confirmed by a study in which ILD prevalence was over 30% in patients over 50 years. Another risk factor is longer disease duration, with an average time of 7.7 years from SLE onset to development of ILD. As other CTDs, NSIP represents the most frequent pattern, although LIP, COP, and UIP have all been found. Regardless of the disease radiological presentation, PFTs remain stable over time: in fact SLE-ILD patients are often characterized by a discrepancy between the absence of respiratory symptoms and the presence of PFT and HRCT abnormalities. Prognosis is quite good in patients with SLE-ILD, with a 5-year survival rate reported at 93% [90]. In contrast, one study found a worse prognosis in SLE patients with lung involvement. Smoking and thrombocytopenia have been linked with worse survival, while radiological NSIP/OP pattern in comparison to NSIP alone has been associated with improved survival in SLE-ILD [91].

Data on treatment of SLE-ILD is particularly limited; a recent survey of SLE experts yielded 90% agreement with the regimen of first-line therapy of corticosteroids with mycophenolate mofetil or cyclophosphamide followed by rituximab [92].

MCTD

Lung involvement is common in MCTD, a CTD characterized by common clinical features of SLE, SSc, RA and/or PM/DM and it is associated to the presence of anti U1-ribonuclear protein (RNP) antibody, previously known as an antibody to extractable nuclear antigen (ENA), in up to 2/3 patients [93]. A definite diagnosis can be delayed, because of the overlapping features of different autoimmune diseases that may develop sequentially. Because of this heterogeneity, most authors describe MCTD as an independent entity, while some believe that it might represent an early stage of a definite connective tissue disease such as SLE or SSc or overlap syndrome.

Pulmonary involvement is a prominent characteristic of MCTD, with HRCT abnormalities reported in 85% of patients, although most of them remain asymptomatic. There is discrepancy about the most frequent imaging features, with some studies reporting a high prevalence of ground glass opacities, and others indicating a much higher prevalence of fibrosis, including honeycombing and traction bronchiectasis.

Anti-Sm antibodies are linked to epitope spreading, a phenomenon that occurs within the first two years after MCTD diagnosis and is characterized by the recognition by a new epitope. Anti-Ro52 antibodies are also associated with MCTD-related

pulmonary fibrosis, showing a HRCT pattern of NSIP in 50-80%. Literature underlines the association between the presence of anti-Ro52 antibodies and the severity of lung fibrosis. Among pulmonary comorbidity, PAH is a leading cause of morbidity and mortality in 29% of MCTD patients, with a prevalence increasing with time [94]. Even if in literature, MCTD-ILD is associated with increased mortality, overall survival is high with a 5-year survival >95%.

Corticosteroids are the mainstay of treatment, together with immunotherapeutic agents such as mycophenolate mofetil or azathioprine. In a cohort study of MCTD-ILD patients treated with rituximab, FVC and DLCO were stable at two years of follow-up [95].

CONCLUSION

CTD and ILD are often closely linked: sometimes lung involvement represents the only clinical feature of autoimmune disorder, while ILD occurs more frequently in the early or late phase of disease. The most frequent HRCT pattern of CTD-ILD is NSIP, expression of pulmonary inflammation, usually responsive to corticosteroids and/or immunosuppressants. Very intriguing, and worthy of further studies, is the relationship between the presence of specific antibodies and clinical severity of lung involvement.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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