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Review Article

Interstitial lung disease in patients with idiopathic inflammatory myopathy (IIM-ILD): Definitions, epidemiology, pathophysiology, clinical manifestations, complications, risk, and mortality factors (narrative review)

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ABSTRACT

Interstitial lung disease refers to a group of disorders generally characterized by progressive scarring of lung tissue due to a wide variety of causes and associated with a plethora of symptoms. Patients with this diagnosis can be asymptomatic or present severe symptoms that could lead to death. Its signs and symptoms are the same in patients with concomitant connective tissue disease and those without. Genetics and immunity play essential roles in patients with interstitial lung disease and idiopathic inflammatory myopathy. Alterations in genes and excessive production of specific cytokines can lead to the development of interstitial lung disease. Interstitial lung disease can have several complications, including chronic respiratory distress and infections, and can worsen the prognosis of patients with idiopathic inflammatory myopathy. Here, we present a narrative review describing the epidemiology, pathophysiology, clinical manifestations, risk factors, and complications of the population with interstitial lung disease and idiopathic inflammatory myopathy.

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Enfermedad pulmonar intersticial en pacientes con miopatía idiopática inflamatoria (EPI-MII): definiciones, epidemiología, fisiopatología, manifestaciones clínicas, complicaciones, factores de riesgo y mortalidad (revisión narrativa)

Palabras clave:
Enfermedad pulmonar intersticial
Miopatía idiopática inflamatoria
Autoanticuerpos
Epidemiología
Manifestaciones clínicas
Mortalidad

RESUMEN

La enfermedad pulmonar intersticial se refiere a un grupo de trastornos generalmente caracterizados por cicatrización progresiva del tejido pulmonar, debidos a una amplia variedad de causas y asociados con múltiples síntomas. Los pacientes con este diagnóstico pueden estar asintomáticos o presentar síntomas severos que podrían conducir a la muerte. Los signos y los síntomas de esta enfermedad son iguales en pacientes que tienen una enfermedad del tejido conectivo concomitante y en aquellos que no la tienen. La genética y la inmunidad desempeñan papeles esenciales en pacientes con enfermedad pulmonar intersticial y miopatía idiopática inflamatoria. Las alteraciones en los genes y la producción excesiva de citoquinas específicas pueden conducir al desarrollo de la enfermedad. A su vez, la enfermedad pulmonar intersticial puede tener varias complicaciones, como dificultad respiratoria crónica e infecciones, y puede empeorar el pronóstico de los pacientes con miopatía idiopática inflamatoria. Presentamos una revisión narrativa que describe la epidemiología, la fisiopatología, las manifestaciones clínicas, los factores de riesgo y las complicaciones de la población con enfermedad pulmonar intersticial y miopatía idiopática inflamatoria.

Introduction

Interstitial lung disease (ILD) encompass a heterogeneous group of conditions that affect the lungs, characterized by varying degrees of inflammatory and/or fibrotic involvement with specific radiological patterns on high-resolution computed tomography and in histopathology in lung biopsy samples, leading to deterioration of lung function and increased morbidity/mortality in patients.[1,2] The respiratory system, especially the lung parenchyma, is a frequent target of autoimmune-mediated injury. Rheumatological diseases can present different forms of pulmonary involvement, one of which is interstitial lung disease associated with connective tissue disease (CTD-ILD).[3]

CTD-ILD is a significant risk factor for morbidity and mortality and represents a diagnostic challenge in the earliest stages,[4] which warrants a multidisciplinary approach. As in other autoimmune diseases, ILD is a complication in patients with idiopathic inflammatory myopathies (IIMs), disorders of unknown etiology that involve different degrees of muscle inflammation. In this review of IIM-ILD, we summarize the essential disease features of this condition and its evolving epidemiology.

Based on the clinical, immunological, and histological characteristics, five groups that make up the IIM complex can be distinguished: overlap myositis (which includes antisynthetase syndrome, aSyS), dermatomyositis (DM), polymyositis (PM), inclusion body myositis, and immune-mediated necrotizing myopathy.[5] We can also include the spectrum of clinically amyopathic dermatomyositis (CADM) or "dermatomyositis sine myositis," characterized by the same skin findings as in DM but without muscle weakness or elevation of muscle enzymes, which confer a higher risk of ILD, the rapid progressive form (RP-ILD).[6] Of the aforementioned subtypes, DM, PM, aSyS, and CADM are frequently associated with ILD.[7]

Methodology

A non-systematic narrative review of the literature was carried based upon available Spanish and English language literature in the PubMed database.

Results

Epidemiology

IIM-ILD was first described in a patient with DM in 1956.[8] By 1974, the prevalence of ILD in DM/PM was estimated at 5%.[9] Since then, the association of IIM with ILD has been established through multiple case series, multicenter studies with highly variable prevalences (from 19.9 to 86%),[10–12] and later meta-analyses and systematic reviews of the literature. The overall prevalence of IIM has been estimated to range from 14.0 to 21.4 cases per 100,000 population in the United States.[13] Sun et al. detected a global prevalence of 41% of ILD presentation in the composite of patients with DM/PM in the first meta-analysis and systematic review, with a predominance in the Asian population (twice that in Europe and America). The prevalences of ILD in the DM, PM, and CADM subtypes, were 42%, 35%, and 53%, respectively, with high heterogeneity between the studies. Based on the data available, ILD has a rising prevalence, probably attributed to a more active

search and the diagnostic tools available.[14] In the most recent meta-analysis by Joy et al., an overall prevalence of IIM-ILD of 41% (95% CI 33–50%) was reported, without specifying prevalences in the clinical subtypes.[15] However, when associated with antibodies against aminoacyl-tRNA synthetase (ARS), the majority exceeds 70%.[16]

Pathophysiology

Lung injury begins with damage to the alveolar epithelial or endothelial cells, allowing an increase in permeability and destruction of the alveolar-capillary membrane. Next, inflammatory cell infiltration at the interstitial space, promoting the infiltration of fibroblasts and the formation of fibrotic foci from the production of extracellular matrix proteins by myofibroblasts.[17,18] Endothelial damage has been proposed as the initial pathway for events in CTD-ILD, potentially through the early growth response protein 1 (EGR1), lysophosphatidic acid receptor 1 (LPAR1), and Wnt/catenin pathways. Oxidative stress and the response to proteins unfolded by cellular stress are related to the endoplasmic reticulum.[19] This damage induces the release of proteins such as surfactant protein D (SP-D) and Krebs von den Lungen protein-6 (KL-6), which have key roles in the prognosis of patients, which will be explained later.

Genetics

Immunogenetics plays an essential role in developing IIM-ILD, and specific subtypes of HLA-DRB1 and tumor necrosis factor alpha have been reported in patients with IIM-ILD. HLA-DRB1*03–DQA1*05–DQB1*02 showed an association with the expression of ILD in patients with DM and patients with PM, in whom it has been associated with the positivity of an antisynthetase antibody.[20] In turn, HLA-B*08.01 favors the cascade of events and includes the presentation of antigens, the priming of CD8+ T cells, and the crosstalk of CD4+ T cells with B cells.[21]

Telomere shortening can hinder the healing and/or turnover of alveolar epithelial cells after an initial injury, and mutations in genes related to leukocyte telomeres have been related to cellular senescence and alteration of the reparative response. Among them is telomerase reverse transcriptase (TERT), telomerase RNA component (TERC), dyskerin pseudouridine synthase 1 (DKC1), telomere elongation regulator helicase 1 (RTEL1), poly-A-specific ribonuclease (PARN), and TERF1-interacting nuclear factor 2 (TINF2).[22] In the case of DM-/PM-ILD, specific susceptibility gene loci have been detected (DQB1*06:02, DRB1*03, DRB1*01:01, DRB1*04:05).[23–25]

Innate immunity

Among the environmental factors related to inflammatory lung injury are gastroesophageal reflux and infections (mainly Epstein–Barr virus, retroviruses, parvoviruses, mycobacteria, *Mycoplasma* spp., and *Borrelia* spp.).[26] In ILD, macrophages can be polarized to become classic proinflammatory M1 macrophages, which secrete proinflammatory and/or profibrotic cytokines (IL-1β, IL-8, IL-10, and CXCL13), or alternative profibrotic M2a macrophages, which secrete profibrotic cytokines (CCL22, PDGF-BB, and IL-6).[18] Ye et al. used a single-sample gene set analysis of variation. They found the type I interferon signaling pathway in the lungs of DM patients with MDA5+ antibodies and a higher score of interferon-stimulated genes (ISG) and fibrosis. Additionally, they observed that fibroblasts had strong interactions of the type I interferon signaling pathway with antibody-secreting cells (ASCs), subsets of CD8+ T cells, and macrophages in the lungs of the DM MDA5+ patient, but not in healthy controls. These data suggest that, in the context of the overactivation of type I interferon signaling, infiltrated immune cells and fibroblasts potentially form a unique profibrotic microenvironment in the lungs of patients with MDA5+ DM.[27]

Extracellular neutrophil traps (NETs), which can lead to the formation of autoantibodies, cause direct damage to epithelial cells and result in increased production of proinflammatory cytokines that induce different NET formation, thus perpetuating the harm (found in PM/DM), in addition to tending to activate pulmonary fibroblasts and differentiate into myofibroblasts.[22] Proteomics analysis shows a significant increase in galactosylated IgG Fc-glucan has been detected in patients with IIM vs. the general population. This finding was not correlated with other extra muscular manifestations, so overexpression may have a specific role in pulmonary involvement. Overexpression has also been found in gelsolin (related to the degradation of actin filaments released by necrotic cells during inflammation) and calgranulin B in patients with overlap syndrome.[28]

Adaptive immunity

T lymphocytes

Preclinical studies have identified profibrotic profiles (Th2, Th17), antifibrotic profiles (Th1, Th22, and γδ-T), and pleiotropic T lymphocytes (Tregs and Th9) as mediators of fibrosis.[29] Lung biopsies of patients with CTD-ILD have shown an increase in T lymphocytes in lung tissue and in lymphoid aggregates. In addition, the bronchoalveolar lavage of patients with IIM has accumulated cytotoxic CD8+ T cells.[30] A cohort study in patients with ILD showed a decrease in blood lymphocytes with a higher ratio of CD4:CD8, which suggests an increase in cytotoxic activity with accelerated cell destruction.[21] In another study, an increase in CD4+ CXCR4+ T cells was detected in the blood and bronchoalveolar lavage of patients with MDA5+ DM, with the ability to promote the proliferation of pulmonary fibroblasts through IL-21, which suggests a potential pathogenic role in MDA5+ DM.[31]

B lymphocytes

An exaggerated ASC response has been found in patients with MDA5+ DM. Ye et al. evaluated the peripheral B-cell compartment by single-cell RNA sequencing: three groups were naive B cells (scB1-Transitional, scB2-ISG, and scB3-Naïve), three were memory B cells (scB4-Unswitched Bm, scB5-Switch Bm [changed Bm], and atypical scB6-Bm), and two were ASCs (scB7-pASC [proliferating] and scB8-rASC [resting]). The MDA5+ DM-Active group showed significantly higher proportions of scB2-ISG, scB7-pASC, and scB8-rASC cells. Furthermore, the proportions of the three groups were strongly reduced in the three MDA5+ DM-Remission patients. The

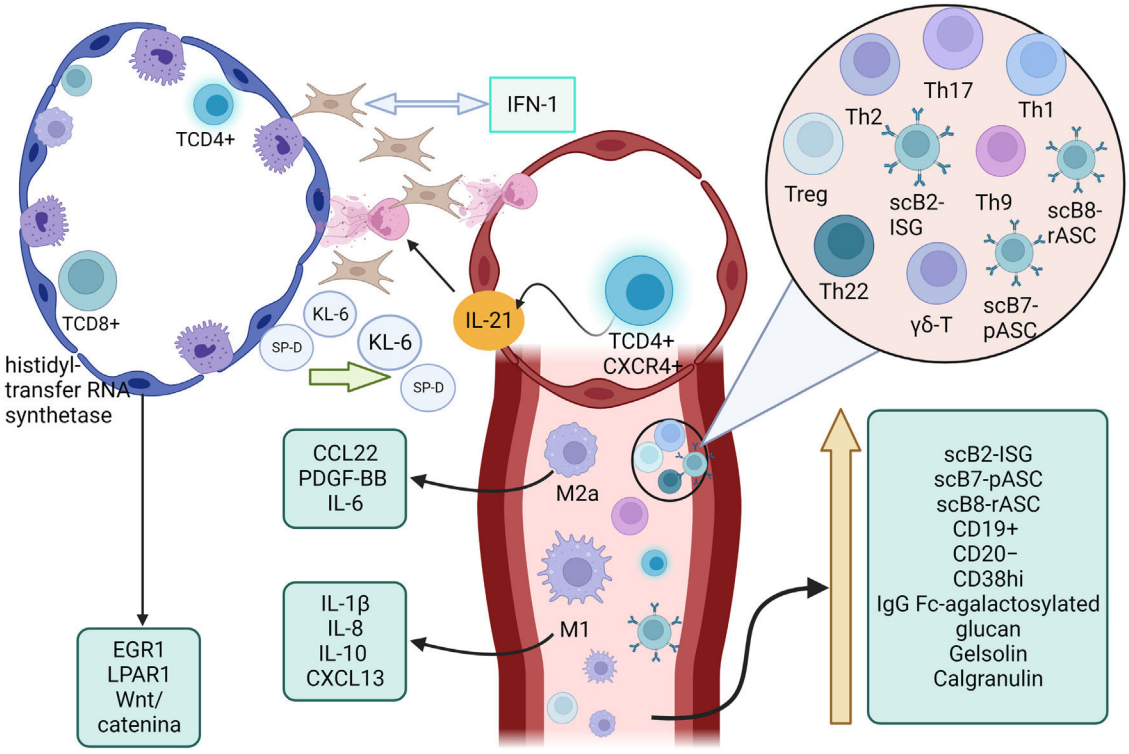

Fig. 1 – Pathophysiology of interstitial lung disease in patients with idiopathic inflammatory myopathy.

frequencies of CD19+CD20−CD38hi were significantly higher in MDA5+ DM-Active patients than in control patients (IIM without ILD) and healthy controls. A high clonal expansion of ASCs was also found in patients with MDA5+ DM-Active.[27]

B-cell activating factor (BAFF), also known as BLys, is a member of the TNF family of cytokines and an important agent in B-cell survival. It has been implicated in pathogenesis and as a biomarker correlated with disease activity in a variety of autoimmune diseases in which antibodies and B cells are believed to be relevant for pathogenesis. In IIM, elevated levels of BAFF have been reported in patients with PM, anti-Jo-1 antibodies and ILD and in patients with DM, regardless of the presence of anti-Jo-1 positivity ILD.[32,33] In Fig. 1, we propose an image illustrating the pathophysiology of ILD in patients with IIM.

Autoantibodies

In patients with IIM-ILD in Latin American population the most frequently detected autoantibodies are anti-Ro-52 and anti-Jo-1.[34] Although myositis-specific autoantibodies (MSAs) and myositis-associated autoantibodies (MAAs) as a whole are not part of the current diagnostic and classification criteria for myositis, it has been recognized that specific autoantibodies confer distinct clinical phenotypes.[35] Despite the aforementioned major importance of autoantibodies in the pathophysiology of IIM-ILD, the 2017 classification criteria of the European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) only incorporated the presence of anti-Jo-1.[2] Therefore, some patients could be misclassified, especially those who are hypo or amyopathic, or patients with ILD, MSA and hypo or amyopathic disease could be classified as having interstitial pneumonia with autoimmune features (IPAF).[36] Table 1 presents the frequency of each autoantibody in ILD, in myositis, mortality, clinical features, and radiological patterns.

Biomarkers

Other biomarkers of ILD activity include lactate dehydrogenase (LDH), Krebs von den Lungen protein-6 (KL-6), serum surfactant protein D (SP-D) and ferritin. KL-6 is a high molecular weight mucin-like glycoprotein expressed in type II alveolar pneumocytes and bronchiolar epithelial cells. Fathi et al. detected significantly more KL-6 in PM/DM patients with ILD than in PM/DM patients without ILD, which was correlated with functional residual capacity and an increased risk of developing ground-glass opacities, diffuse fibrosis and honeycombing.[67] Ihn et al. reported higher levels of SP-D in ILD-DM/PM, with an inverse relationship with FVC and DLCO.[68] Serum ferritin is correlated with the disease activity of CADM-ILD or anti-MDA5+ DM.[32] In a small cohort, a threshold ferritin level greater than or equal to 1600 ng/ml was the most sensitive indicator of survival.[69]

Clinical manifestations

The signs and symptoms related to IIM-ILD do not differ from those of other types of ILD, and it has a variable presentation from asymptomatic forms to exertional dyspnea (50%), nonproductive cough (33%), decreased exercise tolerance, clubbing and asthenia.[5] As in other autoimmune

Table 1 – Autoantibodies and their frequency in interstitial lung disease, myositis, mortality, clinical features and radiological patterns.

Group	Antibody	Antigen	Frequency in ILD	Frequency in myositis	Mortality	Clinical features	Radiological patterns
Myositis-specific antibodies (MSA)	Anti-ARS	Aminoacyl-tRNA synthetase (ARS)	Strong association[37] All ARS: 70%[38] Anti-Jo-1: 66%[38] OR: 11.1[38] Non-Jo-1: 84%[38] Anti-PL12 OR: 4.9 (0.45–53)[39] Anti-PL7 OR: 3.04 (0.6–15.2)[39] Anti EJ: OR: 14.2 (1.69–118.9)[39]	General: 25–42%[40] Anti-Jo-1: DM: 11% PM: 21%[38] Non-Jo-1: DM: 10% PM: 8%[38] Anti-PL7: 5–10%[41] Anti-PL12: <5%[41] Anti EJ: 5–10%[41] Anti OJ: <5%[41] Anti KS: <5%[41] Anti Ho: <1%[41]	49 months survival. ARS-ILD with myositis: 20%[42] ARS-ILD without myositis: 18.8%[42] 5-Years survival Anti-Jo-1: 90%[43] Non-Jo-1: 75%[43]	Lung: chronic or subacute ILD (more severe in anti-PL7, -KS, -OJ, -PL12) Muscle: myositis (mostly in anti-Jo-1, -PL7, -EJ). Skin: Mechanic's hand Others: Raynaud phenomenon, non-erosive arthritis (especially anti-Jo-1), fever[16,44]	NSIP (50%) OP (20%)[5,16] Traction bronchiectasis (75%)[5]
	Anti-MDA5	Melanoma differentiation-associated protein 5 (MDA5)	Strong association[37] 50–100%[16,39,40] OR: 3.109 (1.578–6.128)[39]	~10–20% in DM[16] ~50–70% in CADM[16] Caucasian: 0–13%[45] Asian: 11–57%[45]	6-Months survival: 33–66%[46] 5-Year survival: 56%[47]	Lung: RP-ILD, OR: 25.33. Spontaneous pneumomediastinum or pneumothorax Muscle: Often amyopathic or mild myositis Skin: Gottron's papules, heliotrope rash, ulceration, palmar pustules Others: Raynaud phenomenon[16,44–46]	Mixture of characteristics of NSIP, OP and UIP, without a typical pattern[46]
	Anti-Mi-2	Nucleosome remodeling and deacetylase complex (NuRD)	Weak association[37] 4%[38] OR: 0.18 (0.05–0.58)[39]	4–10% of all myositis[41] DM: 9% PM: 1%[38]	44 months survival: 97.1%[48]	Lung: No known association Muscle: myositis (generally mild) Skin: classic DM rash[44]	Not reported
	Anti-SAE	Small ubiquitin-like modifier activating enzyme	Western: 0–18%[49] Asian: 25–71%[49] General: 21%[50] OR: 5.54 (0.192–160.19)[51]	2–8% of adult DM[7,52]	5%[53] Good response to treatment[49]	Lung: no known association Muscle: may be amyopathic initially Skin: classic DM rash, cutaneous ulcers, dark red/violaceous rash Other: increased cancer associated DM prevalence[44,45,50]	Organizing pneumonia (OP)[54]

Table 1 – (*Continued*)

Group	Antibody	Antigen	Frequency in ILD	Frequency in myositis	Mortality	Clinical features	Radiological patterns
	Anti-NXP2	Nuclear matrix protein 2	Doubtful association[37] Li et al.: OR 0.26 (0.18–0.38)[55] Xing et al.: OR: 1.4 (0.43–4.75)[51]	Adult: 2–17%[56] Caucasian: 14–25%[45] Asian: 2–5%[45]	No connection with poor prognosis[55]	Lung: no known association Muscle: myositis (generally severe, distal weakness, dysphagia) Skin: classic DM rash, calcinosis Other: Peripheral edema. Increased cancer association (3.68-fold increase)[44,45,57]	NSIP, OP[37]
	Anti-HMGCR	3-Hydroxy-3-methylglutaryl CoA reductase	Weak association[37] 1%. OR: 0.05 (0.007–0.451)[39]	Adult: 6%[56]	Limited data	Lung: no known association Muscle: necrotizing myositis Skin: often absent. Statin use association[44]	Not reported[37]
	Anti-SRP	Signal recognition particle (SRP)	Doubtful association[37] 15% (7–25)[38] OR: 2.014 (0.405–10.02)[51]	DM: 1% (1–2)[38] PM: 5% (3–7)[38] 3–10% of all myositis[40] Adult: 2%[56]	10 years survival: 96.4%[58] Good response to therapy	Lung: association with ILD reported[44] Muscle: necrotizing myositis severe and rapidly progressive myositis, severe symmetric proximal muscle disease Skin: Often absent[40]	NSIP[37]
	Anti-TIF1-γ/α	Transcription intermediary factor 1-γ/α (TIF1-γ/α)	Weak association[37] 18% OR: 0.163 (0.080–0.333)[39]	20–29% of DM[40]	Limited data	Lung: negatively associated Muscle: myositis (mild or rarely amyopathic) Skin: classic DM rash, severe skin disease, 'red on white' lesions Other: Strong association with malignancy (up to 75%)[44,45]	Not reported[37]
Myositis-associated antibodies (MAA)	Anti-cN1A	Cytosolic 5′-nucleotidase 1A (cN1A)	Not typical. Limited to case reports	33–37% of IBM[40] Adult: 4–21%[56]	HR 1.95, 95% CI = 1.17–3.27 in IBM[59]	IBM, inclusion body myositis[40]	Not reported

Table 1 – (*Continued*)

Group	Antibody	Antigen	Frequency in ILD	Frequency in myositis	Mortality	Clinical features	Radiological patterns
	Anti-U1-RNP	U1-ribonucleoprotein (U1-RNP)	7% (1–24)[38]	DM: 6%(4–8) PM: 5% (3–7)[38] Adult: 10%[56]	Limited data Good response to therapy[60]	Overlap syndrome, MCTD Raynaud's phenomenon, ILD, PAH[40]	Not reported
	Anti-PM/Scl	PM/Scl100, PM/Scl75	Strong association[37] 38% (25–52)[38]	DM: 9%(6–12)[38] PM: 6% (4–9)[38] 3–10% of all myositis[40]	9.5-Year mortality: 8%[61]	Lung: late onset, chronic Indolent[37] PM-SSc overlap syndrome[40]	NSIP[61]
	Anti-Ku	Components of DNA-dependent protein kinase (Ku70/Ku80)	Doubtful association[37] 27% (8–55)[38] OR: 0.379 (0.06–2.39)[51]	DM: 1 (1–2)[38] PM: 2 (1–3)[38] 2% of all myositis[40]	18%[62]	Lung: refractory to therapy, impacts on prognosis[37] Muscle: overlap syndrome[40] Skin: Raynaud phenomenon[63] Other: arthralgia[63]	Unknown[37]
	Anti-Ro52	TRIM21 located in cytoplasm and nucleus	Strong association[37] OR 3.1, 95% CI 1.3–7.6[51] Isolated: 7%[2]	25–30.9%[54,56] With con concurrent anti-Jo-1 positive: 56–72%[64]	All-cause mortality: 28.8% (composite of patients with anti-Ro52 alone vs. anti-Ro52 plus an additional MSA)[65] 24-Month mortality (in patients with anti-MDA5-positive CADM-ILD): 59.9% vs. 85.7%; $p = 0.051$[66]	Lung: High predictor of ILD, poor outcomes if associated with anti-MDA5 and antisynthetase[37] RP-ILD: 54.8% vs. 23.8%; $p = 0.014$[66]	Chronic, insidious, fibrosing processes, less acute/subacute subtypes[37]

diseases, respiratory manifestations can appear before the appearance of skin or muscle manifestations in 2.7–37.5% of cases[1,70,71] or afterward (up to 40%).[3,72,73]

Particular attention should be paid to the extrapulmonary characteristics of IIMs to distinguish secondary ILD from primary ILD. The evaluation of these patients includes a careful investigation of constitutional symptoms (weight loss and fever, present in up to 20%), respiratory manifestations (bibasal rales on auscultation and reduction of respiratory movements due to muscle weakness), cutaneous manifestations ("climber's foot", "mechanic's hands", Gottron's papules and rash, heliotrope rash, Holster and shawl signs, and Raynaud's phenomenon), articular (seronegative arthritis of the distal joints, with asymmetric and oligoarticular characteristics). Clubbing and hypertrophic osteopathy are rare in IIM-ILD.[74,75]

In 2021, a multidisciplinary consensus of experts was published aiming at the early diagnosis and follow-up of CTD-ILD. One of the recommendations is to recognize signs and symptoms as "red flags" to suspect ILD, including basal Velcro rales on lung auscultation and dry cough with dyspnea on exertion not related to infectious or active cardiovascular disease.[4] Specifically, in IIM-ILD, the clinical presentation can be classified into three patterns based on the respiratory symptoms at presentation: the rapidly progressive form with acute/subacute symptoms (RP-ILD, 18.7–28.8%), chronic with progressive symptoms (51.4–57.7%), and the asymptomatic/subclinical form (11.5–29.9%).[17,76] Deterioration of RP-ILD (expected in less than three months) is defined by two or more of the following: symptomatic exacerbation (dyspnea on exertion), increase in the severity of abnormalities in the parenchyma on HRCT, and worsening of lung function parameters (10% in forced vital capacity or ten mmHg in the partial pressure of oxygen).[2,77]

A clear relationship has been found between CADM and ILD. Mukae et al. compared the clinical presentation of ILD in patients with CADM and DM, finding a much shorter time of respiratory symptoms before hospital admission (4.6 vs. 34.1 months), a greater rate of PR-ILD (64 vs. 19%), and higher mortality (45 vs. 6%, all in the acute compromise subgroup).[78] Fewer than 20% of patients with DM and PM have this presentation.[3] The chronic form presents with dyspnea of insidious appearance and nonproductive cough with rare constitutional symptoms. Radiographically, it can appear as organized pneumonia (OP) or overlap of OP with nonspecific interstitial pneumonia (NSIP) with an excellent response to glucocorticoids and a chronic fibrosing form, which corresponds to fibrotic NSIP or usual interstitial pneumonia (UIP), which tends to respond poorly to glucocorticoids and other types of immunosuppression.[79] The presence of radiological, and physiological defines the asymptomatic or subclinical form, and, in some cases, subtle or histopathological abnormalities in asymptomatic patients with symptoms that have not been attributed to ILD[80]; it appears in DM and PM in 30% of patients.[72,81]

Complications

The complications derived from IIM-ILD are many and include chronic respiratory failure, respiratory and gastrointestinal opportunistic infections (with a mortality of 28%), hypoventilation and hypercapnia in the context of muscle dysfunction, microaspirations with risk of aspiration pneumonia/pneumonitis, type 1 pulmonary hypertension (associated with connective tissue disease), and type 3 pulmonary hypertension (mediated by pulmonary involvement). Finally, pneumomediastinum occurs in 15% of IIM-ILD patients and has a high mortality rate.[5,79] The appearance of opportunistic infections in IIM-ILD is significant and could at least be associated with the disease itself and its treatments. Thus, preventive therapy of *Pneumocystis jirovecii* should be prescribed as soon as patients receive glucocorticoids at equivalent doses of prednisolone >20 mg/d for >4 weeks, especially for the most severe cases.[82,83]

Risk factors and prognosis

It is clinically of considerable importance to identify antibodies in patients with PM/DM, because each is closely associated with certain clinical features. Older age of presentation,[84,85] arthralgia,[15,84,85] fever,[85] elevated acute-phase reactants (erythrocyte sedimentation rate, C-reactive protein),[15,85] Afro-descendant ethnicity, presence of mechanical hands, lateral erythema of the hip, anti-ARS, anti-MDA5, antinuclear antibodies (ANA), anti-Sjögren syndrome type B (anti-SSB) antibodies, and anti-Ro52 are independent risk factors for developing IIM-ILD.[15] ILD was observed more frequently in patients with anti-EJ (OR 14.202, 95% CI 1.696–118.902), anti-Jo-1 (OR 11.111, 95% CI 3.306–37.335), and anti-MDA5 antibodies (OR 3.109, 95% CI 1.578–6.128). Patients with ILD who had anti-HMGCR seemed less likely to develop ILD, which suggests that anti-HMGCR could help protect against ILD in patients with IIM.[39]

Anti-Mi-2 (OR 0.180, 95% CI 0.055–0.589), anti-TIF1-γ (OR 0.163, 95% CI 0.080–0.333), and anti-HMGCR (OR 0.058, 95% CI 0.007–0.451) were protective factors against the development of ILD.[39] ANAs, anti-Ro52, or SSA did not significantly alter mortality.[86,87] In the Latin American cohort of Alberti et al., none of the clinical or antibody variables were statistically significant for poor baseline lung function in multivariate analysis.[34] The prevalence of anti-MDA5 and anti-Ro-52 was significantly higher in DM/PM with ILD than in DM/PM without ILD (anti-MDA5, 45.57 vs. 0.00%, respectively, $p < 0.001$; anti-Ro-52, 60.76 vs. 26.09%, respectively, $p < 0.001$). In contrast, the prevalence of anti-TIF1-γ and anti-NXP2 was significantly lower in DM/PM with ILD than in DM/PM without ILD (anti-TIF1-γ, 3.80 vs. 19.57%, respectively, $p = 0.01$; anti-NXP2, 1.27 vs. 10.87%, respectively, $p = 0.047$). No significant difference was observed in the prevalence of anti-Mi-2α, anti-Mi-2β, anti-SAE1, anti-SRP, anti-Ku, anti-PM-Scl75, or anti-PM-Scl100 in DM/PM patients with ILD vs. DM/PM patients without ILD (anti-Mi-2α, 6.33 vs. 4.35%; anti-Mi-2β, 7.59 vs. 0.00%; anti-SAE1, 0.00 vs. 4.35%; anti-SRP, 2.53 vs. 2.17%; anti-Ku, 3.80 vs. 2.17%; anti-PM-Scl75, 2.53 vs. 0.00%; PMScl100, 1.27 vs. 0.00%).[88]

Although the rates of ILD are high in patients positive for anti-ARS, these patients tend to have a better overall prognosis, with a better response to therapy and higher overall survival rates than patients with anti-ARS-negative IIM-ILD.[35] Patients positive for non-Jo-1 anti-ARS have reduced overall

survival compared to patients positive for anti-Jo-1. In a study of more than 200 patients, Aggarwal et al. reported that patients with anti-Jo-1 had a 5-year survival of 90% vs. 75% in patients with non-anti-Jo-1 anti-ARS.[2] Patients positive for anti-PL7 and anti-PL12 have a high prevalence of lung disease (60–90%). They are strongly associated with milder and rapidly resolving myositis but with early and severe ILD.[89] Ro52 and Ro60 are part of a ribonucleoprotein complex called SSA/Ro. Still, only antibodies against the Ro52 subunit are considered markers of IIM and are found in up to 56% of patients positive for anti-Jo-1.[89] La Corte et al. reported that patients with coexisting anti-Ro52 antibodies have more severe pulmonary symptoms and greater ILD than those without.[90]

De Lorenzo et al. reported higher FVC readings in patients with anti-PM/Scl antibodies than in those with anti-ARS antibodies, with less decline in lung function over time. Similarly, a good clinical course has been observed in scleroderma ILD associated with anti-PM/Scl antibodies compared to anti-Scl70 antibodies. Although ILD can manifest early in anti-PM/Scl disease, it occurs more frequently in later stages of the natural history and is strongly associated with cutaneous manifestations.[2] In a study in China, the ILD frequency was 35.29% vs. 66.67% in patients positive vs. negative for anti-NXP2 antibodies. All the findings of HRCT showed image characteristics of nonspecific interstitial pneumonia and/or organized pneumonia, and no cases of RP-ILD were observed.[91] Authors such as Gossez hold that the measurement of anti-NXP2 should be part of assessing ILD in patients with suspected DM.[92] Although all such studies have had small sample sizes, a meta-analysis found that the prevalence of ILD in patients positive for anti-Ku ranged from 8% to 55%. ILD is not strongly associated with anti-Mi-2; Lega et al. reported an average ILD prevalence of 4% in 154 seropositive patients. In a review of 226 patients with anti-U1-RNP and IIM antibodies, only 7% had ILD.[2,38] The prevalence of specific antibodies for Ks, Ha, Zoα, and cN1A was 1.3%, 2.0%, 1.4%, and 0.9%, respectively, in ILD.[93]

The prevalence of ILD among patients positive for anti-SAE1 varies from 50 to 71%,[49,94–96] being the highest in Asian populations. ILD is usually mild, with few respiratory symptoms, despite abnormalities on imaging. The characteristics of ILD in anti-SAE1 patients on HRCT are predominantly peripheral subpleural ground-glass opacities corresponding to organized pneumonia.[94,95] Li et al. sought to distinguish DM/PM with ILD from DM/PM without ILD, and the sensitivity, specificity, and positive predictive value for anti-MDA5 were 45.57, 100.00, and 100.00%, respectively, while those for anti-Ro-52 were 60.76, 73.91, and 80.00%, respectively.[88]

Mortality

Significant heterogeneity in the literature regarding reported mortality, ranging from 7.5% to 55%.[71,87,97–99] The mortality rates for PM-ILD, DM-ILD, and CADM-ILD are reportedly 16.7%, 24.4%, and 37.2%, respectively.[12,84,98,99] Despite early mortality in severe forms, the 5-year survival rate in IIM-ILD is >85%. However, some patients may worsen during the first year of treatment; the time until disease progression is usually counted in years. As an example, in a long-term follow-up series, 20% of patients with IIM-ILD (not including patients with anti-MDA5 antibodies) worsened despite immunosuppressive treatments, and the other patients were stable (35–55%) or improved (25–45%).[5]

With data collected from the Multicenter Retrospective Cohort of Japanese Patients with myositis-Associated ILD (JAMI), Gono et al. created a prognostic prediction model for patients with DM-/PM-ILD. They found that the combination of C-reactive protein >0.8 mg/dL and KL-6 >1000 U/ml in patients with anti-MDA5 was associated with a mortality risk of more than 50%.[100] Regarding mortality, African-descended ethnicity,[89] anti-MDA5,[39,86,87] age, male sex,[86,87] acute/subacute onset,[87] amyopathic clinical disease,[84,87] dyspnea, fever, elevated C-reactive protein, LDH, ground-glass opacities,[86] ulcers,[85] ferritin,[86,87] albumin,[84,86] reduced %TLCO, and %CV,[86,87] cardiac involvement[84] carry high risk.

Conclusions

Since the first descriptions of IIM-ILD, our understanding of its pathophysiology and clinical phenotypes have grown. Recognizing the risk and prognostic factors has undoubtedly changed the approach to this rare clinical presentation.

Authors' contributions

AHJ conceived the idea and design of the study. AHJ, LFT, TDM, and CJVP searched for information in databases. All authors contributed substantially to the writing of the manuscript and approved the submitted version.

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Conflicts of interest

The authors declare no conflicts of interest.

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