Diagnosis and treatment of interstitial lung disease related to systemic autoimmune myopathies: a narrative review

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SUMMARY

Systemic autoimmune myopathies (SAMs) are rare diseases that lead to muscle inflammation and may be associated with a variety of systemic manifestations. Although there is great heterogeneity in the spectrum of extra-muscular involvement in SAMs, interstitial lung disease (ILD) is the most frequent lung manifestation. SAM-related ILD (SAM-ILD) presents significant variations according to geographic location and temporal trends and is associated with increased morbidity and mortality. Several myositis autoantibodies have been discovered over the last decades, including antibodies targeting aminoacyl-tRNA synthetase enzymes, which are associated with a variable risk of developing ILD and a myriad of other clinical features. In this review, the most relevant topics regarding clinical manifestations, risk factors, diagnostic tests, autoantibodies, treatment, and prognosis of SAM-ILD are highlighted. We searched PubMed for relevant articles published in English, Portuguese, or Spanish from January 2002 to September 2022. The most common SAM-ILD patterns are nonspecific interstitial pneumonia and organizing pneumonia. The combination of clinical, functional, laboratory, and tomographic features is usually sufficient for diagnostic confirmation, without the need for additional invasive methods. Glucocorticoids remain the first-line treatment for SAM-ILD, although other traditional immunosuppressants, such as azathioprine, mycophenolate, and cyclophosphamide have demonstrated some efficacy and, therefore, have an important role as steroid-sparing agents.

Key words: *Diagnosis, drug therapy, inflammatory myopathies, interstitial lung diseases, myositis.*

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INTRODUCTION

Interstitial lung disease (ILD) is a hallmark of lung involvement in systemic autoimmune myopathies (SAMs). Pooled data from a recent meta-analysis indicated that the global prevalence of ILD in patients with SAMs is around 40%, with important variations according to geographical location, time trends, myopathy subtype, and presence of malignancy (1, 2). SAM-related ILD (SAM-ILD) is associated with increased mortality, with a 10-year survival rate of 81%, compared to 90% in patients without ILD (3, 4). It is important to establish the differential ILD diagnosis with other causes of respiratory manifestations in patients with SAM, including infection, drug-induced pneumonitis, spontaneous pneumomediastinum, respiratory muscle involvement, cardi-

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ac dysfunction, and pulmonary hypertension. Early detection, careful follow-up, recognition of features that suggest rapidly progressive ILD (RP-ILD), and aggressive treatment of lesions with poorer prognosis are essential to improve the SAM-ILD outcomes (5-7).
The purpose of this narrative review is to describe the clinical, radiological, and antibody profiles of SAM-ILD. This review also addresses diagnostic tests, risk factors, prognosis, and the most recent evidence on recommended treatments for this frequent organ manifestation of autoimmune myopathies.

MATERIALS AND METHODS

We searched PubMed using the terms ((“myositis” [Mesh] or “polymyositis” or “dermatomyositis” or “antisynthetase syndrome”) and (“lung diseases, interstitial” [Mesh] or “interstitial lung disease”)) for articles published in English, Portuguese, or Spanish from January 1, 2002, to September 30, 2022. From a total of 1674 articles, 46 relevant articles about the clinical manifestations, risk factors, diagnosis, treatment, and prognosis of SAM-ILD were included. In addition, the reference lists of the included studies were manually searched for additional eligible studies, resulting in a total of 88 articles included in this narrative review.

Table I - Clinical manifestations of interstitial lung disease (ILD) and characteristics associated with an increased risk of ILD in systemic autoimmune myopathies.

Parameters	Characteristics associated with ILD
Disease onset	Older age at disease onset
Acute	Gottron’s papules
Subacute	Ethnicity/race (Black)
Chronic	Elevated ESR and CRP
Behavior	Hypoalbuminemia
Progressive	Elevated serum IgM
Non-progressive	Arthritis or arthralgia
Signs and symptoms	Fever
Cough	Antisynthetase antibodies
Dyspnea	Anti-MDA-5 antibodies
Fatigue	Anti-Ro-52 antibodies
Reduced physical performance	Absence of associated malignancy
Crackles at lung bases	
Others	
Asymptomatic lung disease (common)	
May precede muscle involvement	
Lung-dominant phenotype (amyopathic or hypomyopathic cases)	
Infections (pneumonia, recurrent aspiration pneumonia)	

ILD, interstitial lung disease; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IgM, immunoglobulin M.

RESULTS

Clinical manifestations

Pulmonary involvement in SAMs is variable, ranging from asymptomatic to life-threatening conditions (8-10) (Table I). Approximately 18.7% of patients present an acute symptomatic ILD, while others may present a chronic progressive course or may even have an asymptomatic evolution. Patients may rarely present rapid disease progression (9). ILD may occur before, concomitantly, or after the identification of muscle involvement. Particularly in antisynthetase syndrome, clinical features at the onset are highly variable, and ILD may be the initial disease manifestation and responsible for the most disabling symptoms (10, 11).
Clinicians should consider the possibility of dissociation between the pulmonary and the muscular involvements, since amyopathic and hypomyopathic phenotypes may be associated with severe forms of ILD (2). In approximately 20% of the cases, ILD precedes muscle involvement (3, 4, 12). ILD symptoms are usually non-specific and include a non-productive cough, dyspnea, fatigue, and reduced physical performance, which may have an acute or insidious onset. Additionally, the muscle weakness associated with SAM may also determine the impact on the degree of dyspnea. Crackles at the lung bases are the most common findings in the physical examination (11).

Risk factors

Several characteristics have been described as risk factors for developing SAM-ILD (13-16). A systematic review with meta-analysis found that older age at disease onset, arthritis or arthralgia, fever, anti-Jo1 and anti-MDA-5 antibodies, and elevated

levels of acute phase reactants like erythrocyte sedimentation rate and C-reactive protein were risk factors for SAM-ILD (16). Interestingly, malignancy reduced the risk of SAM-ILD (16). A Chinese cohort with 286 SAM patients identified older age at disease onset, anti-Ro-52 antibody, Gottron's papules, elevated serum immunoglobulin M levels, and hypoalbuminemia as risk factors for SAM-ILD (13). Additionally, black ethnicity was associated with SAM-ILD in a British cohort of 107 patients (14). Anti-MDA-5 and anti-PL-7 antibodies are associated with RP-ILD, and fever and lymphopenia are associated with RP-ILD phenotype among patients positive for anti-MDA-5 antibodies (15). The main risk factors for ILD in SAMs and the several clinical manifestations of SAM-ILD are summarized in Table I.

Imaging and histological features

Imaging plays an important role in the initial evaluation and follow-up of SAM-ILD. High-resolution computed tomography (HRCT) is the method of choice not only to diagnose and identify the extent or the pattern of ILD but also to assess response to treatment. A variety of tomographic findings have been described, including ground-glass and reticular opacities, consolidations, peribronchovascular thickening, honeycombing, and linear opacities that mainly affect the lung bases. HRCT should be performed in supine and prone positions to exclude areas of gravity-induced atelectasis (17).

Imaging and histological patterns of particular interest in SAM-ILD are nonspecific interstitial pneumonia (NSIP), organizing pneumonia (OP), usual interstitial pneumonia (UIP), and coexisting patterns, which have been re-

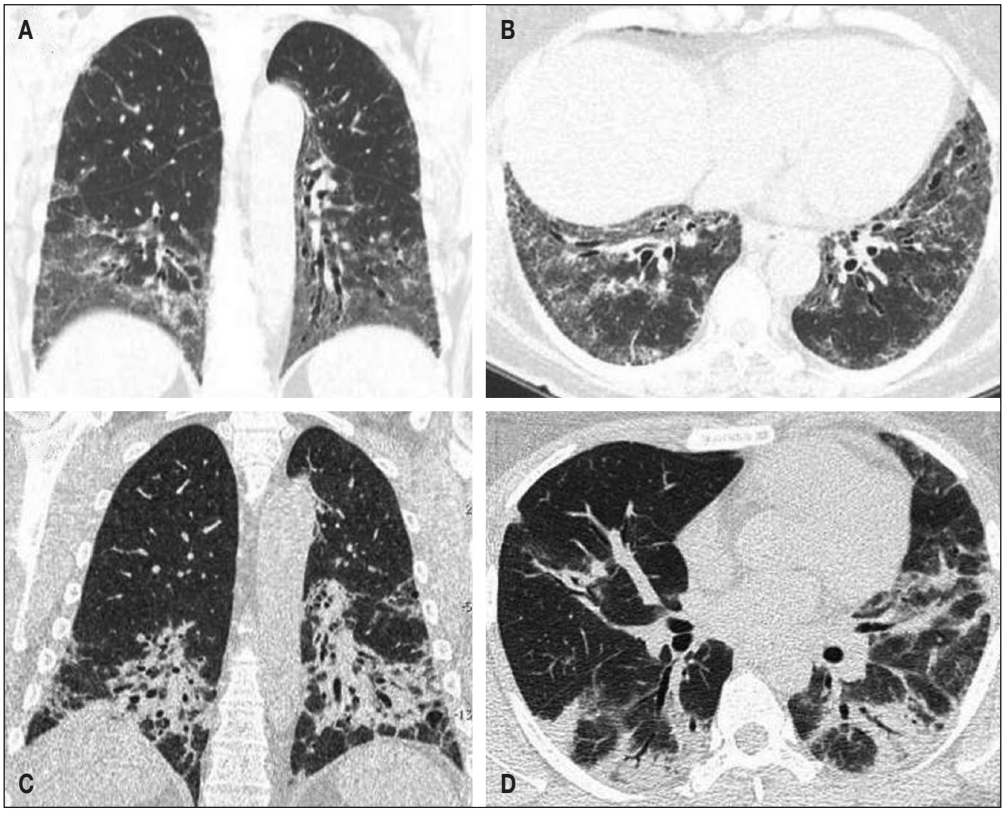

Figure 1 - A, B: Coronal and axial chest computed tomography (CT) images from a patient with nonspecific interstitial pneumonia associated with antisynthetase syndrome show bilateral and predominantly lower lobe ground-glass opacities and traction bronchiectasis; C, D: Coronal and axial chest CT images from a patient with polymyositis and organizing pneumonia demonstrate areas of consolidation in the lower lung lobes, predominantly peripheral and along the perobroncovascular axis.

ported with variable incidence according to disease subtype and autoantibodies.

Nonspecific interstitial pneumonia (NSIP) is the most common pattern of SAM-ILD in most of the cohorts (18, 19). This pattern is characterized in the HRCT by bilateral and predominantly lower lobe ground-glass and irregular reticular opacities associated with traction bronchiectasis, peribronchovascular extension, and relative subpleural sparing (Figures 1A and B) (20, 21). Histologically, it is evidenced by alveolar wall thickening, varying degrees of interstitial inflammatory infiltrate, and varying amounts of uniform fibrosis with preservation of alveolar architecture (20, 21).

Formally known as bronchiolitis obliterans with organizing pneumonia (OP), OP is a pattern of pulmonary tissue repair (22). HRCT usually identifies patchy areas of consolidation suggestive of OP, predominantly peripheral and along the peribronchovascular axis (Figures 1C and D) (22). Histologically, buds of fibroblasts, inflammatory cells, and loose connective-tissue matrix (Masson's bodies) are found filling the alveoli, alveolar ducts, and respiratory bronchioles (22, 23). When there is no identifiable etiology, OP is named cryptogenic. Not rarely, coexisting histological and/or imaging patterns of ILD, particularly the overlap between NSIP and OP, have been reported in the same systemic disease (19, 24).

Usual interstitial pneumonia (UIP) is an infrequent pattern of SAM-ILD compared to NSIP or OP (25). HRCT findings compati-

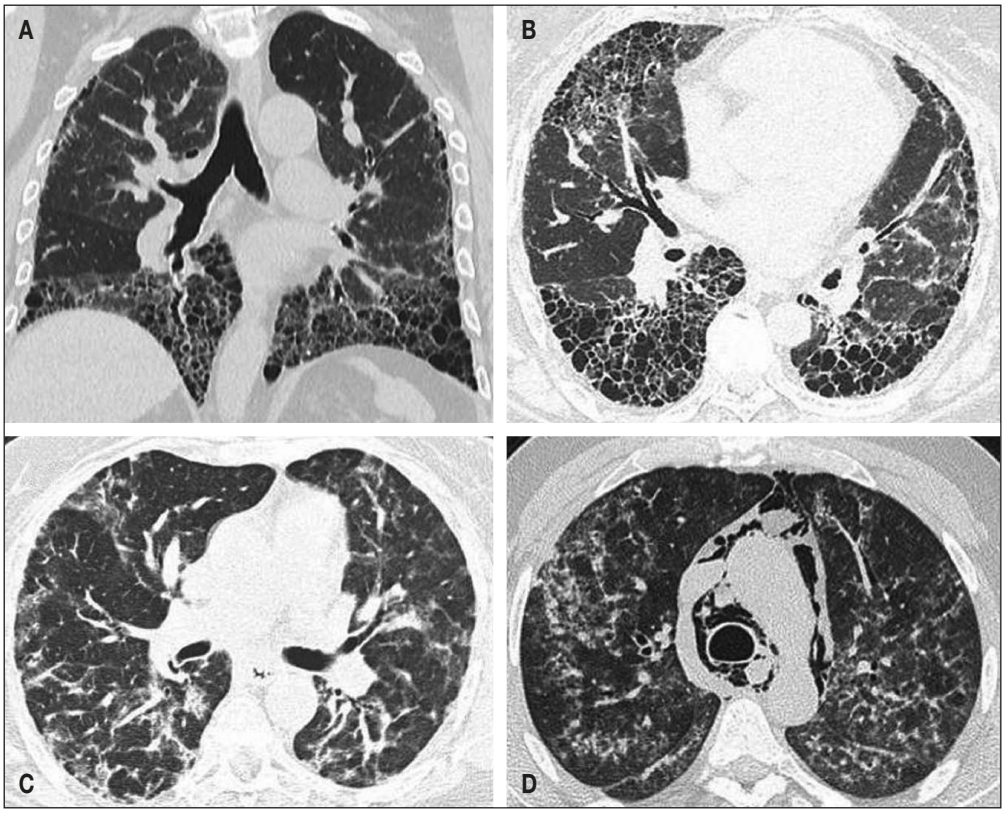

Figure 2 - A, B: Coronal and axial chest CT images from a patient with nonspecific interstitial pneumonia associated with polymyositis show subpleural and bibasilar predominant honeycombing changes, and traction bronchiectasis, with discrete areas of ground-glass opacities; C: Axial chest CT image from a patient with polymyositis and acute interstitial pneumonia demonstrates diffuse areas of ground-glass opacities and consolidations; D: Axial chest CT image from a patient with dermatomyositis demonstrates a pneumomediastinum and diffuse areas of ground-glass opacities and consolidations compatible with acute interstitial pneumonia.

ble with the typical UIP pattern include subpleural and basal predominant reticular opacities and honeycombing changes. Ground-glass opacities can be seen, but they are typically less extensive than reticular abnormalities (26). Three signs in HRCT are more common in UIP associated with connective tissue disease than in idiopathic pulmonary fibrosis: the straight-edge sign, which consists in the isolation of fibrosis to the lung bases with sharp demarcation in the craniocaudal plane; the exuberant honeycombing sign, which is characterized by more than 70% lung areas having this pattern; and the anterior upper lobe sign, which consists in a concentration of fibrosis within the anterior aspect of the upper lobes concomitant with lower lobe involvement (27). Histologically, there are areas of scarred fibrosis, alveolar collapse, cystic changes, and architectural distortion with abrupt transition to normal or less affected parenchyma. Inflammation is mild or absent and fibroblastic foci (organizing connective tissue with proliferating fibroblasts and myofibroblasts) may be seen juxtaposed to fibrotic zones (26, 28).

A subgroup of patients with SAMs may present characteristics of RP-ILD evolving with acute hypoxemic respiratory failure, consistent with AIP, quite similar to patients with acute respiratory distress syndrome (28). In this scenario, HRCT can demonstrate patchy bilateral opacities, septal thickening, and consolidation, which is more frequently distributed in a gravitationally dependent gradient (Figures 2C and D). Histological findings are usually consistent with extensive diffuse alveolar damage (DAD) (29, 30).

Spontaneous pneumomediastinum is a rare manifestation of SAM probably caused by parenchymal distortion secondary to ILD manifested by worsening of previous dyspnea and chest pain (31) (Figure 2D). The imaging and histological findings of the main patterns of ILD are described in Table II.

A lung biopsy is usually not necessary to confirm the diagnosis of SAM-ILD, which may be determined by the combination of clinical, functional, laboratory, and tomographic features. Lung biopsy may be performed in the suspicion of infection or malignancy, with atypical manifestations, or in the lack of treatment response (5-7).

Pulmonary function tests and bronchoalveolar lavage

A restrictive pattern on spirometry is the most common functional example identified in SAM-ILD, with reduced total lung capacity, forced vital capacity (FVC), and carbon monoxide diffusing capacity, and an FVC<60% is associated with more severe

Table II - Imaging and histological patterns of particular interest in interstitial lung disease related to systemic autoimmune myopathies.

Type	High-resolution CT	Histology (lung biopsy)
NSIP (the most common)	Bilateral and predominantly lower lobes ground-glass and irregular reticular opacities associated with traction bronchiectasis, peribronchovascular extension, and relative subpleural sparing	Alveolar wall thickening, varying degrees of interstitial inflammatory infiltrate, and varying amounts of uniform fibrosis with preservation of alveolar architecture
OP	Patchy areas of consolidation, predominantly peripheral and along the peribronchovascular axis	Buds of fibroblasts, inflammatory cells, and loose connective-tissue matrix are found filling the alveoli, alveolar ducts, and respiratory bronchioles
UIP	Subpleural and basal predominant reticular opacities and honeycombing changes. Ground-glass opacities can be seen, but they are typically less extensive than reticular abnormalities. Three signs may be seen: the straight edge, the exuberant honeycombing, and the anterior upper lobe	Areas of scarred fibrosis, alveolar collapse, cystic changes, and architectural distortion with abrupt transition to normal or less affected parenchyma. Inflammation is mild or absent and fibroblastic foci may be seen juxtaposed with fibrotic zones
RP-ILD	Patchy bilateral opacities, septal thickening, and consolidation, which are more frequently distributed in a gravitationally dependent gradient	Extensive DAD

CT, computed tomography; DAD, diffuse alveolar damage; NSIP, non-specific interstitial pneumonia; OP, organizing pneumonia, UIP, usual interstitial pneumonia; RP-ILD, rapidly progressive interstitial lung disease.

disease and worse prognosis (32, 33). Pulmonary function tests (PFT) should be performed at baseline and during follow-up to assess the disease course and response to treatment.

In patients with SAM, the associated use of PFT together with HRCT can help to elucidate the cause of dyspnea, which may be multifactorial in origin, sometimes making it difficult to distinguish between parenchymal lung disease and respiratory muscle weakness.

Table III - Autoantibodies, interstitial lung disease, and additional features in systemic autoimmune myopathies.

Autoantibodies	Frequency in adult patients with SAMs (%)	Frequency of ILD (%)	Disease pattern (%)	Clinical manifestations
Anti-Jo1	15-30	70-80	35 UIP 10 NSIP 5 OP 50 DAD	Arthritis, mechanics' hands, myositis
Anti-PL7	5-10	84	50 UIP 25 OP 25 NSIP	Heliotrope rash, severe ILD, myositis, pericardial effusions
Anti-PL12	<5	90	67 UIP 17 NSIP 17 OP	Less likely to develop myositis, RP, isolated ILD
Anti-KS	1	90	27-35 UIP 62 NSIP	Less likely to develop myositis, Isolated ILD
Anti-OJ	1	8		Severe myopathies, lower incidence of RP.
Anti-EJ	1	>90	52 NSIP 21 OP 23 NSIP+OP 2-10 UIP	Fever, mechanic's hands, muscle involvement, RP
Anti-Ha	<1	<1	21 UIP	ILD, myositis
Anti-Zo	<1	60-100	60 NSIP 30 OP 10 UIP	ILD, myositis, arthritis, RP, and mechanics' hands
Anti-Mi-2	4-10	4-38		Classic DM, arthritis, RP, lower incidence of malignancy
Anti-NPX-2	2-30	3		Skin calcification in JDM, muscle pain/weakness.
Anti-MDA-5	7-14 ADM (80 CADM)	European: 60 Asian: 90	20 NSIP 13 NSIP+OP 50 OP	CADM, RP-ILD, cutaneous ulcerations, and typical rashes of DM
Anti-TIF1γ	20-30	<10		Adult malignancy-associated DM, JDM
Anti-SRP	3-13	10-20		Acute onset necrotizing myopathy, resistant to treatment, recurrent
Anti-SAE	<10	<10	OP	DM, severe cutaneous involvement and typically precedes the muscular involvement
Anti-Ro52	10-40	7-50		Typical rashes (Gottron's sign, heliotrope rash, and mechanic's hands
Anti-U1RNP	6-10	7-50		Overlap syndrome, MCTD, RP, ILD, PAH
Anti-PM/Scl70	3-10	25-80		PM-SSc overlap syndrome
Anti-Ku	<2	27-80		Overlap syndrome, dysphagia

SAMs, systemic autoimmune myopathies; ILD, interstitial lung disease; UIP, usual interstitial pneumonia; NSIP, nonspecific interstitial pneumonia; OP, organizing pneumonia; DAD diffuse alveolar damage; RP, Raynaud's phenomenon; RP-ILD, rapidly progressive interstitial lung disease; DM, dermatomyositis; JDM, juvenile dermatomyositis; MCTD, mixed connective tissue disease; PAH, pulmonary arterial hypertension; PM, polymyositis; SSc, systemic sclerosis; CADM, clinically amyopathic dermatomyositis; ADM, amyopathic dermatomyositis; CAM, cancer-associated myositis; HRCT, high-resolution computed tomography.

Bronchoalveolar lavage may be used to rule out infections, including tuberculosis, pneumocystis, and other fungal infections when these clinical suspicions are present in patients with SAMs (34).

Autoantibodies and the lung

Traditionally, autoantibodies found in patients with SAMs are described as myositis-specific autoantibodies (MSAs) or myositis-associated autoantibodies. Certain MSAs are more closely associated with lung disease in patients with SAMs (35-43).

In clinically amyopathic dermatomyositis (CADM), the presence of anti-MDA-5 is associated with an increased likelihood of amyopathic disease and increased risk of ILD, including an RP-ILD phenotype, with high morbidity and mortality (36, 37).

The anti-Jo-1 antibody is the most common anti-aminoacyl tRNA synthetase (anti-ARS) antibody, occurring in approximately 20% of patients with SAMs (35, 38). This anti-ARS antibody is strongly associated with ILD, Raynaud's phenomenon, arthritis, and mechanic's hands (38). Other anti-ARS antibodies include antibodies against the PL-7, PL-12, OJ, EJ, KS, Zo, and Ha antigens. Noteworthily, anti-Jo-1 and other anti-ARS antibodies, such as anti-PL-12, have been observed in some patients with ILD who lack evidence of myositis (38).

Anti-Ro-52 autoantibodies have been suggested as a risk factor for the development of ILD in some studies (39, 40). In the context of SAMs, anti-Ro-52 has been more commonly reported in patients with anti-ARS antibodies (39, 40).

Anti-PM/Scl antibodies can be found in patients with overlap syndromes, especially polymyositis and systemic sclerosis, and have been linked to the following manifestations: myositis, Raynaud's phenomenon, inflammatory arthritis, and ILD, which may have a poor prognosis (35). Another antibody, found in 1-3% of patients with polymyositis (PM) and dermatomyositis (DM), is the anti-Ku, which has been linked to a high risk of developing ILD, with a poor response to glucocorticoids (41).

Anti-Mi-2 antibodies are associated with a relatively acute onset of DM, traditionally associated with a classic shaw-sign or V-sign, and may respond well to therapy (42, 43). Anti-Mi-2 is associated with a lower chance of developing ILD, less muscle involvement and malignancy, better response to immunosuppressive drug use, and, therefore, a better prognosis (42, 43).

A detailed description of myositis-specific and -associated autoantibodies with their respective frequency, relationship with ILD, and other clinical manifestations are summarized in Table III.

Treatment of systemic autoimmune myopathies related interstitial lung disease

Currently, no randomized controlled trial has assessed the best initial treatment for SAM-ILD, or other pulmonary manifestations related to SAMs (44) (Table IV). A systematic review and meta-analysis of SAM-ILD treatment included 27 highly heterogeneous studies of limited methodological quality and concluded that the best initial treatment remains elusive, with an urge for trials, especially on RP-ILD (44).

Five guidelines have already addressed the treatment of SAM-ILD (45-49) and recommendations are based mainly on retrospective studies and expert opinions. The Brazilian Society of Rheumatology guidelines for the treatment of SAMs briefly cites ILD as a severe manifestation of SAMs that may require intravenous methylprednisolone (IVMP) pulse therapy, as well as intravenous immunoglobulin (IVIg) either as first-line treatment or in refractory cases. These treatments are followed by maintenance therapy, preferably with a combination of immunosuppressive drugs (45). The Australian/New Zealand (46) and Japanese (47) guidelines on the treatment of ILD related to connective tissue diseases (CTD) specifically address SAM-ILD, and both propose treatment algorithms based on disease onset (acute, subacute, or chronic), behavior (progressive or non-progressive), and antibody profile (anti-MDA-5). A Spanish group published specific treatment guidelines for RP-ILD associated with anti-MDA5 antibodies (48) and the British Society of Rheumatology recently published guidelines for pedi-

Table IV - Treatment options for interstitial lung disease related to systemic autoimmune myopathies.

Condition	Treatment
Asymptomatic, chronic non-progressive ILD	Follow-up, usually no pharmacological treatment is required
Acute, subacute, or chronic progressive ILD	Prednisone 0.5-1 mg/kg daily (or equivalent), taper gradually
	Consider early association with a steroid-sparing agent like AZA 2-3 mg/kg/day or MMF 2-3 g/day
	Calcineurin inhibitors (TAC and CSA) are alternatives to AZA and MMF
Severe or refractory ILD	IVMP 0.5-1 g/day for three to five days, repeat every 21-28 days until significant improvement
	IVIg 2 g/kg divided over three to five days, consider if concurrent severe skin rash, dysphagia, or muscle weakness
	Cyclophosphamide: prefer intravenous over oral due to a better safety profile
	Rituximab 1 g on day zero and day 14, repeat every 6 months
	Lung transplantation
Specific antibody profiles	Anti-MDA-5: consider initial triple therapy (IVMP, cyclophosphamide, and calcineurin inhibitor)
	Antisynthetase antibodies: consider a more aggressive therapy
Progressive fibrosing ILD phenotype	Antifibrotic agents (nintedanib and possibly pirfenidone) in addition to immunosuppressive drugs
Other potential therapeutic drugs	Tocilizumab, abatacept, tofacitinib, anakinra, and basiliximab
Not recommended	Methotrexate: risk of pneumonitis TNF-inhibitors: risk of drug-induced ILD and autoimmune myositis
Non-pharmacological treatment	Recommended in all cases Education of patient and caregiver Physical exercises to improve fatigue, pain, and quality of life

AZA, azathioprine; CSA, cyclosporine; ILD, interstitial lung disease; IVIg, intravenous immunoglobulin; IVMP, intravenous methylprednisolone; MMF, mycophenolate mofetil; TAC, tacrolimus; TNF, tumor necrosis factor.

atric and adult patients with SAMs (49).

The need to initiate treatment in SAM-ILD is usually based on the severity of respiratory impairment and the degree of progression. Glucocorticoids are usually the initial treatment of SAM-ILD regardless of the pattern of ILD. In either acute, subacute, or chronic progressive SAM-ILD, it is usually indicated to start 0.5-1 mg/kg daily of prednisone or equivalent in association with azathioprine 2-3 mg/kg/day or mycophenolate mofetil 2-3 g/day (45). Glucocorticoids need to be slowly tapered. Considering the high rate of complications associated with the prolonged use of glucocorticoids and the elevated risk of disease exacerbation during glucocorticoid monotherapy withdrawal, a combination with an immunosuppressive drug is widely recommended as an initial treatment (45). Second-line agents are calcineurin inhibitors, such as tacrolimus (0.05-0.08 mg/kg/day) and cyclosporine (2-4 mg/kg/day) which can be used as monotherapy or in combination with azathioprine or mycophenolate mofetil. The use of methotrexate in SAM-ILD has been described (50), but it is usually avoided due to the risk of pneumonitis, even though this event is rare (<1%) (50, 51).

Patients with signs of respiratory failure or extensive disease suggestive of RP-ILD may require IVMP 0.5-1 g/day for three to five days. This scheme can be repeated every 21-28 days until a significant improvement is achieved. Despite the limited evidence, it is possible to associate IVIg 2 g/kg divided over three to five days to reduce the risk of infections related to IVMP, achieve faster recovery, decrease the necessity of glucocorticoids, and avoid long-term sequelae of SAMs (52, 53).

Cyclophosphamide is one of the most studied medications in SAM-ILD, considered as an option in rapidly progressive forms with respiratory failure, although it is usually reserved for ILD refractory to other immunosuppressive drugs due to concerns of serious adverse effects, such as infections

and bladder toxicity (26). A systematic review (44) showed a lower efficacy of cyclophosphamide in chronic ILD compared to other immunosuppressive drugs such as calcineurin inhibitors, probably due to a selection bias (more severely disabled patients were allocated to receive cyclophosphamide).

Personalized treatment based on antibody profiles and other prognostic factors would be of great benefit to these patients. Currently, guidelines suggest more aggressive treatment for the anti-MDA-5 subgroup (46-48). However, the disease phenotype may vary among different ethnicities, as shown in a multicenter study of anti-MDA-5 positive patients from Latin America, where no association between anti-MDA-5 and ILD or RP-ILD was found (54). The same is true for anti-ARS antibodies, which may exhibit different severity profiles among different ethnicities (55). Therefore, we do not recommend defining a treatment strategy based solely on antibody profiles.

While most SAM-ILD patients present with an NSIP or OP pattern and respond to treatment, some develop a progressive fibrosing phenotype (18). New antifibrotic agents such as nintedanib and pirfenidone have shown promising results in the treatment of diseases with progressive pulmonary fibrotic phenotypes, despite treatment with immunosuppressant drugs (56). In a trial including 170 CTD-ILD patients, but only two patients with SAMs, nintedanib reduced the rate of FVC decline in comparison with the placebo (57). Therefore, additional studies are warranted to assess the role of antifibrotics in progressive fibrotic phenotypes in patients with SAM-ILD.

It is also worth mentioning that some patients are refractory to treatment, with severe and progressive disease, and may require lung transplantation. To optimize the success of surgery, some variables, such as gastroesophageal reflux, kidney disease, skin ulcers, myocardial disorders, and pulmonary hypertension, should be considered, as they are related to increased morbimortality (47).

The education of individuals with SAM-ILD and their caregivers about their condition and prognosis is of great importance in improving their quality of life and optimizing care planning (45, 46). Physical exercise is highly encouraged, as it improves several symptoms (*e.g.*, fatigue and pain) and overall quality of life (58).

The immunomodulatory effects of tumor necrosis factor (TNF) inhibitors have been used in various autoimmune diseases. However, there have been reports of immune disorders associated with the use of TNF inhibitors, including myositis and ILD (59-62). Initial case reports and series reported improvements in muscle strength, pulmonary symptoms (61), and laboratory findings (63) with infliximab; however, a larger series with more severe pulmonary involvement did not report such findings (64). A case series of patients treated with either infliximab or etanercept reported that one of the patients had prior evidence of mild lung fibrosis with no evidence of improvement after treatment with a TNF blocker, but it is unclear which agent was used (65). In summary, anti-TNF drugs are currently not indicated for pulmonary involvement of SAMs.

Concerning abatacept, the ARTEMIS study did not specifically evaluate pulmonary disease; the only parameter that could assess this manifestation was the pulmonary disease activity visual analog scale, a component of the international myositis assessment and clinical studies group core set measures. Changes in this component were not statistically significant (66). A phase 2 randomized controlled trial of abatacept in ILD with the antisynthetase syndrome is ongoing (ClinicalTrials.gov identifier: NCT03215927), and the primary outcome is the difference in FVC change from baseline to 24 weeks (67).

Regarding tocilizumab in SAMs, the largest study was an open-label pilot study with patients with refractory immune-mediated necrotizing myopathy, in which 7 out of 11 patients responded well to treatment. Although two patients had ILD, the authors did not mention whether these patients had any response in the pulmonary domain (68). Another study with tocilizumab was a retrospective cohort of Chinese patients

with the antisynthetase syndrome, demonstrating that four out of five patients treated with an intravenous standard dose of 8 mg/kg every 4 weeks achieved a good response, all of whom were anti-PL-7 positive (69).
Rituximab is the immunobiological agent of choice for patients with refractory SAM-ILD. In line with this, a recent meta-analysis of four studies on ILD and myositis concluded that rituximab was moderately effective as a second-line therapeutic strategy with a functional improvement rate of 76% in 37 patients with chronic ILD, like other immunosuppressants, such as cyclosporine, azathioprine, and tacrolimus (44). Several case reports and case series of patients with antisynthetase syndrome have reported rituximab to be an effective therapy (69-74). The RECITAL study was designed to compare rituximab (1 g given twice at an interval of two weeks) with intravenous cyclophosphamide (dose of 600 mg/m^2 body surface area given every 4 weeks for a total of 6 doses). The results of this study are expected to improve the evidence on the efficacy of rituximab and cyclophosphamide in the treatment of CTD-ILD (75).
While alemtuzumab has not been promising in a case report (76), basiliximab (77), anakinra (78, 79), and tofacitinib (80-83) have been described in case reports and case series as therapeutic opportunities for refractory lung conditions.
The main treatment options for SAM-ILD are described in Table IV.

Prognosis

Some characteristics have been associated with a worse prognosis in SAM-ILD, including acute/subacute onset of ILD (*versus* chronic), reduced FVC, advanced age at diagnosis, high concentration of neutrophils in bronchoalveolar lavage, the extent of lung parenchyma involvement by ground-glass opacities on HRCT, and the CADM subtype 80. Despite the poor prognosis of severe acute/subacute SAM-ILD cases, chronic forms usually have a better prognosis with a 5-year survival rate greater than 85% (84, 85).
In addition to the above-mentioned factors, high serum ferritin, elevated C-reactive protein, anti-MDA-5 antibody, serum Krebs von den Lungen-6 (KL-6), male sex, severe infections, diagnostic delay, heliotrope rash, Raynaud's phenomenon, malignancy, mediastinal and subcutaneous emphysema, increased serum aspartate aminotransferase and increased neutrophil/lymphocyte ratio have been identified as independent predictors for mortality in SAM-ILD patients (13, 86-88).

CONCLUSIONS

In conclusion, this narrative review describes the clinical, radiological, tomographic, and antibody profiles of SAM-ILD. This study also addressed diagnostic tests, risk factors, prognosis, and the most recent evidence on recommended treatments for this frequent organ manifestation of autoimmune myopathies.

Expert opinion

The most common SAM-ILD patterns are NSIP and OP. The combination of clinical, functional, laboratory, and tomographic features is usually sufficient for diagnostic confirmation, without the need for additional invasive methods. Glucocorticoids remain the first-line treatment for SAM-ILD, although other traditional immunosuppressants, such as azathioprine, mycophenolate, and cyclophosphamide have demonstrated efficacy and, therefore, have an important role as steroid-sparing agents.

Contributions

All authors contributed equally.

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Conflict of interest

The authors declare no potential conflict of interest.

Availability of data and materials

Data and materials are available by the authors.

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