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ABSTRACT

Diagnosis of interstitial lung diseases (ILD) can be challenging, and the identification of an associated connective tissue disease (CTD) is crucial to estimate prognosis and establish the optimal treatment approach. Diagnostic delay, limited expertise and fragmented care are barriers that impede the delivery of comprehensive healthcare for patients with rare, complex and multiorgan diseases such as CTD and ILD.

In this article we present our perspective on the interdisciplinary diagnosis and interprofessional treatment of patients with ILD and suspected CTD or CTD at risk for ILD. We outline the structure of our service, delineating the roles and responsibilities of the team members. Additionally, we provide an overview of our patient population including diagnostic approaches and specific treatments and illustrate a patient case. Furthermore, we focus on specific benefits and challenges of joint interdisciplinary and interprofessional patient consultations. The importance of rheumatology and pulmonology assessments in specific patient populations is emphasized. Finally, we explore future directions and discuss potential strategies to improve care delivery for patients with CTD-ILD.

INTRODUCTION

Interstitial lung diseases (ILD) damage the lung parenchyma in varying degrees of inflammation and fibrosis and can cause severe symptoms, limitations in physical performance and quality of life in affected individuals.[1] In 16-35% of ILDs there is an associated connective tissue disease (CTD) that is either known before ILD diagnosis or detected at the time of ILD evaluation.[2-4] Depending on the specific CTD, up to 85% of patients have a subclinical, and up to 25% a clinically manifest ILD.[5] ILD carries a significant burden of morbidity and mortality in patients with CTD; in systemic sclerosis (SSc) for example, ILD is the most frequent cause of death,[6] and similarly in rheumatoid arthritis (RA) mortality risks doubles if patients suffer from an associated ILD.[7] Other CTDs where ILD is a frequent organ manifestation include idiopathic inflammatory myopathies (IIM; i.e. polymyositis, dermatomyositis, anti-synthetase syndrome), Sjögren's syndrome (SS) and mixed connective tissue disease (MCTD), with systemic lupus erythematosus (SLE) presenting rarely with ILD.[5]

Diagnosis of CTD-ILDs can be challenging as patients frequently present with unspecific symptoms such as exercise intolerance. Screening CTD patients at risk for ILD or screening those with ILD for CTD has not been widely implemented in clinical routine, and some patients present with symptoms of ILD months to years before the clinical signs of extrapulmonary CTD.[8] There is relevant delay from first symptoms to diagnosis of multiple rheumatological diseases as well as different types of ILD, which might be due to a lack of awareness among physicians and the public.[9-11]

Complex and rare diseases affecting multiple organ systems also challenge treatment and their multifaceted nature calls for specialized, coordinated care across various medical disciplines. Limited expertise, fragmented care delivery, delayed diagnoses, high costs, and

limited access to orphan drugs are barriers that can negatively impact patient outcomes.[12] However, innovative approaches based on the chronic care model, have the potential to overcome such barriers.[13-15]

In this article we address our approach to interdisciplinary diagnosis and interprofessional treatment of patients with ILD and suspected CTD or CTD at risk for ILD. We discuss benefits and challenges of joint interdisciplinary and interprofessional patient consultations.

JOINT CONSULTATIONS PULMONOLOGY – RHEUMATOLOGY

In the following paragraphs we describe the organizational structure and specify roles and responsibilities of the individual members in our joint interdisciplinary patient consultations.

Organisation and Team

In our tertiary referral center for ILD and systemic inflammatory diseases, joint consultations between specialized pulmonologists and rheumatologists were traditionally only performed informally on an individual as-needed basis. In September 2021, SG and BM have initiated a pilot project for a formal interdisciplinary and interprofessional consultation pulmonology-rheumatology**.** The main goal was to address the growing demand for a comprehensive evaluation of complex patients with CTD and suspected or known ILD or patients with unclassifiable ILD and suspected CTD. Patients are typically referred from primary care physicians (general practitioners) or secondary care pulmonologists or rheumatologists in private practice (**Figure 1**). Patients are triaged and consultations are planned by the ILD specialist. Some cases are discussed in multidisciplinary team discussion (MDD) prior to the joint consultation. In weekly clinics, typically four patients are allocated to either a resident in pulmonology or a resident in rheumatology depending on the primary referral question.

Designed as an outpatient half-day assessment, diagnostic tests are performed as needed prior to the consultation, including blood tests, chest CT scans, pulmonary function tests, 6-minute walk tests, cardiopulmonary exercise testing, echocardiography, nailfold capillaroscopy, sicca tests, sonography of joints or salivary glands and/or X-rays of hands and/or feet. Following a resident consultation, findings are discussed together with the senior pulmonologist and rheumatologist in presence of the patient, caregivers and the specialized nurse. Recommendations for further diagnostic tests and treatments as well as open questions are then discussed with the patient. The CTD phenotype, extent, and severity of disease manifestations, risk for underlying malignancies, and the past or anticipated disease course are taken into consideration for treatment decisions (**Figure 2**). Complex patients can present for joint follow-up consultations after 3-6 months; however, most patients are followed up either by the pulmonologists or the rheumatologists in specialized programs for ILD and CTD, respectively.

Roles of pulmonologists & rheumatologists

The residents are tasked with a thorough questioning of the patient including exposure and medication history as well as specific CTD symptoms, followed by a comprehensive physical examination. Subsequently, the senior rheumatologist re-evaluates the patient for extrapulmonary CTD signs and symptoms, including examination of skin, salivary glands, lymph nodes, vasculature, joints, musculature, and nervous system. Both specialists review available information and diagnostic tests, discuss the case with all parties, and suggest further approaches to the case. The pulmonologist is typically responsible for the introduction of inhalation therapy, long-term oxygen therapy, antifibrotic therapy and treatment of pulmonary hypertension, while the rheumatologist takes a leading role regarding the immune modulatory treatment. Extrapulmonary disease manifestations are thereby taken into account as wells as

risk factors for progressive disease. Potential benefits from cardiopulmonary and musculoskeletal physical therapy or rehabilitation are discussed together.

Role of the specialized nurse

Patients facing a complex illness require holistic support, which includes facilitating self-management and providing psychosocial support, coordinating care, and establishing networks. Specialized nurses actively participate in our consultations, for example by supporting initiation and adjustments of medications. Nurses bridge the divide between acute and chronic illness management, focusing on care coordination, patient education, and fostering self-management capabilities. Moreover, our nurses assume a pivotal role in addressing the psycho-social dimensions of patient needs, striving to facilitate the integration of the disease management into patients' daily lives in collaboration with caregivers and families.

Multidisciplinary team discussion

We typically discuss our ILD patients at weekly MDDs, which is the recommended reference for ILD diagnosis.[1,16,17] The hour-long meetings are attended by a senior ILD specialist (chair and protocol), a rheumatologist, radiologist, pathologist, specialized nurse and other invited specialists (e.g., cardiologist) as needed, participants can also attend virtually. Cases from pulmonologists or rheumatologists in private practice are typically presented at MDD by the referring physicians themselves or by the ILD specialist before we decide that a joint consultation pulmonology-rheumatology is needed. This helps triage and the organisation of diagnostic tests that are needed before the interdisciplinary consultation.

OUR EXPERIENCE

Patient population

Over the last two years we assessed 170 patients in our joint consultation (**Table 1**). Patients were most frequently referred by secondary care pulmonologists and general practitioners for the evaluation of ILD with suspected CTD (40% of cases) or known CTD with suspected ILD (28% of cases). All patients had pulmonary function tests and chest CT scans performed, almost all echocardiography, and the majority nailfold capillaroscopy and sicca testing. All patients had available immunological serologies with 61% showing positive antinuclear antibodies (ANA). Salivary gland biopsies are rarely performed if there is a clinical suspicion for Sjögren's syndrome. Similarly, cardiovascular MRI, muscle MRI and muscle biopsies are only performed in selected cases with suspected myositis. Bronchoalveolar lavage (BAL) and/or endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) are performed to exclude infection or investigate for malignancy, and transbronchial lung cryobiopsies or surgical lung biopsies are reserved for ILD patients who remain unclassifiable after extensive non-invasive tests.

After the interdisciplinary consultation, 22 (13%) patients had a diagnosis of SSc, 14 (8%) sarcoidosis, 11 (6%) IIM, 9 (5%) RA, 7 (4%) Sjögren's syndrome and 7 (4%) ANCA associated vasculitis. In addition, 9 (5%) patients had overlap syndromes, and 13 (8%) met the proposed criteria of interstitial pneumonia with autoimmune features (IPAF).[18] No evidence of systemic disease was found in 65 (38%) patients with ILD who were diagnosed with unclassifiable ILD. There was no evidence of ILD in only 7 (4%) patients. Of the 68 patients who were referred with ILD and suspected CTD, 8 (12%) were diagnosed with a specific CTD, 12 (18%) had IPAF and 48 (71%) unclassifiable ILD without autoimmune features.

In the joint consultation, a new immunosuppressive treatment was initiated in 27 (16%) patients, at least one immunosuppressive medication was stopped in 14 (8%) and any dose

adjustments took place in an additional 20 (12%) patients. Antifibrotic treatment (nintedanib) was initiated in 14 (8%) patients (**Table 2**). A case example of a patient with anti-Jo-1 positive Antisynthetase Syndrome is illustrated in **Figures 3** and **4**.

The patient experience

We interviewed several patients on their experience with the joint consultations. Patients expressed that they appreciate the well-coordinated schedules without the need for extra appointments, although the half-day programs were tiring for some. The low threshold to ask questions and address uncertainties during consultations and the active involvement in decisions-making, provided a sense of feeling well-cared for, being taken seriously, and feeling well-informed. Patients valued receiving clear advice from two specialists at the same time. Furthermore, the ease of reaching out to the specialized nurses after the consultations gave patients and caregivers an additional sense of support.

DISCUSSION

In our joint pulmonology-rheumatology consultation we evaluated 170 patients over the last 2 years. Systemic disease was excluded in 70% of cases referred with unclassified ILD and suspected CTD. The remaining patients received a specific CTD diagnosis (12%) or working diagnosis of IPAF (18%). The high number of unclassifiable cases before and even after our elaborate assessments reflects a population of ILD patients in whom the determination of a specific ILD is particularly challenging.[19] In these unclassifiable cases, a phenotypic and individual approach to treatment is recommended.[20] We experienced that the interdisciplinary joint consultations are not only valuable for diagnosis but also to determine the individual treatment approach with the estimated optimal benefit to risk ratio. In 75 (44%) patients the

immunosuppressive or antifibrotic ILD treatment was adapted during the consultation. Moreover, we encountered many advantages on the physician, specialized nurse and patient level with only a few challenges with establishing the joint pulmonology-rheumatology consultation.

What are the specific advantages and challenges associated with joint consultations?

Patients benefit from the collective expertise and consolidated management plan of specialists in pulmonology and rheumatology. In the context of rare diseases where typically little diagnostic guidelines are available and few specific therapies are approved, the in-depth clinical expertise plays a pivotal role in improving the quality of patient management and ultimately patient outcome. The accuracy of and the confidence in specific CTD-ILD diagnoses may be improved by combining the pulmonology and rheumatology perspective and expertise.

Interdisciplinary teams provide a more comprehensive and personalized approach to patient care. Multi-organ manifestations, comorbidities, and potential adverse effects of immune modulation such as compromised vaccination responses, increased risk for infections, premature atherosclerosis, bone loss or sarcopenia are considered and if needed managed together with the referring physicians. Specialized nurses add an additional focus on psycho-social aspects and play a key role in patient education which promotes self-efficacy and empowers patients and caregivers. The access to cutting-edge research and novel treatments are also facilitated by a widened spectrum of clinical trials that are available to patients. On a practical level, individually tailored half-day diagnostic assessments avoid multiple sequential appointments for patients, and likely reduce time from referral to final diagnosis. Not only patients but also healthcare professionals report a substantial benefit from the joint consultation, for example our physicians report that being part of a collaborative

interdisciplinary team boosts their job satisfaction, fosters professional growth, career development and networking. Interdisciplinary consultations provide a unique opportunity for pulmonologists and rheumatologists to learn from their colleagues. Senior physicians benefit from this form of continuing education, while residents can enhance their training, deepen their learning in the fields of CTD and ILD, and improve their interdisciplinary communication skills. Lastly, the regular interdisciplinary communication fosters innovation in clinical care, education, training, and research. In our institution for example, scientists from multiple fields join for the multidisciplinary translational research team for lung precision medicine.

While the joint consultations offer numerous benefits, they can come with specific challenges that should be anticipated before implementing an interdisciplinary service. Coordination of schedules and comprehensive assessments is time consuming and resource intensive. Joint consultations require more time and personnel resources than single-specialty consultations, which needs to be considered depending on local reimbursement regulations. However, joint consultations tend to be more time and resource-efficient than multiple individual consultations, making them a potential means of containing healthcare costs. Lastly, fostering favorable team dynamics and a goal-oriented communication to resolve varying opinions needs to be encouraged.

Should patients with ILD be evaluated by a rheumatologist?

MDD is the reference standard for ILD diagnosis where the available clinical, radiological, and pathological information is integrated and MDD members agree on the most likely specific ILD diagnosis.[17] It is recommended to estimate and document the diagnostic confidence in the specific ILD. A diagnostic confidence of ≥90% corresponds to a confident diagnosis and 51-89% to a provisional diagnosis, respectively. If no diagnosis is considered more likely than not (diagnostic confidence ≤50%) the ILD remains unclassifiable.[16,20] Although rheumatologists can

help to reduce the number of unclassifiable cases and provide a CTD-ILD diagnosis,[21] a global survey on MDD practices revealed that only one third of multidisciplinary teams include a rheumatologist.[22] We strongly support that rheumatologists routinely attend MDDs and provide input if a CTD-ILD is suspected, for example based on symptoms or positive autoimmune serologies. We recommend obtaining routine serology for rheumatoid factor, anti-cyclic citrullinated peptide, ANA, and CTD-specific antibodies based on clinical suspicion. Awareness should be raised for auto-antibody negative subtypes of CTDs and the fact that numerous myositis-specific autoantibodies have an anti-cytoplasmatic and not an anti-nuclear pattern when screening with indirect immunofluorescence. Furthermore, rheumatoid factor or ANA at low titres may occur in healthy individuals, particularly elderly populations, and may be positive in the presence of e.g. organ-specific autoimmune diseases, infections, neoplasms, or drugs.[23] Additional laboratory signs that can be associated with CTD include positive inflammatory markers (CRP, blood sedimentation rate), changes of white blood count (anemia, lymphopenia, or thrombopenia), compromised renal or hepatic functional parameters, elevated muscle or heart enzymes, reduced complement components (C3, C4), proteinuria, or polyclonal hypergammaglobulinemia. Furthermore, we recommend a rheumatological evaluation and if possible joint consultations in all patients with unclassifiable ILD, provided that a specific ILD diagnosis might change the therapeutic approach in a specific patient. Lastly, rheumatologists typically have a vast experience with immunosuppressive treatments from which pulmonologists and patients with CTD-ILD can benefit from.

Should patients with systemic autoimmune diseases be evaluated by a pulmonologist?

Patients diagnosed with CTDs that have a high prevalence of ILD such as SSc, MCTD, certain subtypes of IIM or Sjöegren's syndrome should be screened for lung involvement before presenting respiratory symptoms. Dyspnea on exertion, exercise intolerance, fatigue or

presence of crackles on auscultations are signs of advanced pulmonary disease. As lung involvement has a large impact on morbidity and mortality, early diagnosis should be the goal, and individual risk factors for ILD should be considered.[11,24] Pulmonologists provide valuable input with respect to diagnosis and severity staging of ILD, identification and treatment of accompanying complications such as pulmonary hypertension. Furthermore, they are key to determine the indications for inhalation therapies, long-term oxygen treatment, anti-fibrotic treatment, lung transplantation and palliative care approaches. The joint decision-making regarding treatment options and monitoring ensures a coordinated, through management approach for the individual patient.

OPEN QUESTIONS & FUTURE DIRECTIONS

Due to the considerable delay in diagnosing ILDs overall, and specifically CTD-ILD,[9-11] it is crucial to enhance awareness among rheumatologists regarding ILD and among pulmonologists regarding CTD. Teaching pulmonologist to look for subtle signs and symptoms of CTD, the diagnostic value of serological antibody testing and interpretation of nailfold capillaroscopy might contribute to shortening diagnostic delays. Screening for ILD is still controversial for some subpopulations of patients with autoimmune diseases. For example, RA is highly prevalent in the general population and a diagnosis of ILD doubles mortality risk in these patients.[7] However, the proportion of RA patients suffering from relevant ILD is lower than in other CTDs and strategies on how to choose RA patients for ILD screening still need to be established. Given the higher risk for ILD in men and smokers with RA, we support ILD screening in most of these patients.[25]

Specifics of care delivery in patients with (suspected) CTD-ILD still need to be established. The Chronic Care Model has been developed to foster collaborative partnerships among diverse healthcare professionals and aims to enhance the quality and safety of care services.[15] By integrating multiple interdependent elements, including patient self-management support, decision support, clinical information system, and delivery system design,[15] care of patients with chronic illnesses can be improved.[14,26] This promising approach still needs to be evaluated for a potential implementation in ILD services. Moreover, it is important to assess cost-effectiveness of joint consultations and their potential socioeconomic benefits. This would ensure a broader support from diverse stakeholders and facilitate the promotion and sustainability of these services across various health care settings.

Lastly, joint pulmonology-rheumatology services offer a unique opportunity to address research questions for example by establishing longitudinal cohorts and biobanks. Education can be promoted by offering interdisciplinary and interprofessional graduate and postgraduate courses and symposia, organizing patient education events and involvement of the general public.

CONCLUSION

Interdisciplinary collaboration between pulmonology and rheumatology can benefit patients, healthcare professionals, and ultimately society. In general, interdisciplinary and interprofessional work contributes to a more fulfilling work environment with a culture of collaboration, innovation and continuous education. Specifically, physicians and specialized nurses can broaden their perspective and improve their knowledge skills in CTD-ILD. Patients benefit from the expertise of both disciplines and a better coordinated and personalized communication and care, which is particularly important in complex diseases with many

uncertainties. Interdisciplinary consultations might also shorten the delay to diagnosis and treatment by reducing the need for multiple separate appointments and evaluations by specialists who frequently communicate poorly among each other. However, the joint consultations are resource-intensive and demand a high level of organizational work, and the implementation of interdisciplinary consultations may face reimbursement challenges in some healthcare settings. Future work is needed to demonstrate evidence-based effectiveness and the sustainable implementation of this complex intervention.[27]

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TABLES

Table 1. Patient characteristics

n= 170[1]	**Number of patients (%)**
Age, mean (SD)	65 (12)
Sex, women	86 (51%)
Reason for referral	
ILD with suspected CTD	68 (40%)
CTD with suspected ILD	47 (28%)
Others	55 (32%)
Referring physicians	
Primary Care Physician	67 (39%)
Pulmonologist	68 (40%)
Rheumatologist	25 (15%)
Others	10 (6%)
Diagnostic tests performed	
Nailfold Videocapillaroscopy	111 (65%)
Sicca Tests	96 (56%)
Echocardiography	156 (92%)
MDD available	100 (59%)
Diagnosis at follow-up	
Systemic sclerosis	22 (13%)
Primary Sjögren's syndrome	7 (4%)
Rheumatoid Arthritis	9 (5%)
Idiopathic inflammatory myopathy[2]	11 (6%)
Sarcoidosis	14 (8%)
ANCA associated vasculitis	7 (4%)
IPAF	13 (8%)
Overlap Syndromes[3]	9 (5%)
Other ILD[4]	6 (4%)
Unclassifiable ILD	65 (38%)
No ILD[5]	7 (4%)
Concomitant P(A)H	
Suspected in TTE	56 (33%)
Confirmed in RHC	32 (19%)
Radiological pattern	
UIP	29 (17%)
NSIP or OP	78 (46%)
Other ILD pattern	61 (36%)
No ILD	2 (1%)

Time since first manifestation	
Pulmonary	42 months
Extrapulmonary	48 months
FUNCTIONAL TESTS	
FVC, %-predicted, mean (SD)	78 (21)
DLCO, %-predicted, mean (SD)	63 (24)
6MWD, %-predicted, mean (SD)	86 (21)
SEROLOGICAL TESTS	
ANA ≥1:160	104 (61%)
HEP2 cytoplasm pos. (n=150)	70 (47%)
Rheumatoid factor (n=150)	49 (33%)
CCP (n=134)	13 (10%)
SSA Ro60 (n=142)	23 (16%)
SSA Ro52 (n=140)	24 (17%)
SSB (n=134)	8 (6%)
Myositis-specific antibodies[6]	
Jo-1 (n=111)	5 (5%)
PL-7 (n=94)	1 (1%)
PL-12 (n=94)	2 (2%)
EJ (n=92)	1 (1%)
SRP (n=93)	2 (2%)
MDA-5 (n=91)	1 (1%)
SAE1 (n=87)	2 (2%)
NXP2 (n=89)	1 (1%)
SSc-specific antibodies	
Scl70 (n=116)	11 (9%)
ACA (n=74)	8 (11%)
RNA PM III (n=65)	3 (5%)

[1] Number of patients indicated (n) where information was not available for all 170 patients, % as fraction of available tests

[2] Antisynthetase syndrome, dermatomyositis, polymyositis, immune-mediated necrotizing myopathy

[3] Overlap syndromes between systemic sclerosis, Sjögren's syndrome, rheumatoid arthritis and sarcoidosis

[4] Granulomatous lymphocytic interstitial pneumopathy with common variable immune deficiency (CVID) (n=1), systemic lupus erythematosus associated ILD (n=1), silicosis (n=1), lymphangioleiomyomatosis (n=1), organizing pneumonia with CVID (n=1), IgG4 associated ILD (n=1)

[5] CTD associated pulmonary arterial hypertension (n=2), thoracic lymphadenopathy of unknown etiology (n=1), inflammatory syndrome of unknown etiology (n=1), relapsing

polychondritis (n=1), multifactorial exertional dyspnea (n=1), chronic obstructive pulmonary disease (n=1)

[6] Mi2, TIF1 gamma, SAE2, Ku, PmScl and U1RNP without any positive result in the tested patients.

Abbreviations: ACA; anti-centromere antibodies; ANA, antinuclear antibodies; ANCA, antineutrophilic cytoplasmic antibody; CCP, anti-cyclic citrullinated peptide; CTD, connective tissue disease; DLCO, diffusing capacity of the lungs for carbon monoxide; EBUS-TBNA, endobronchial ultrasound-guided transbronchial needle aspiration; FVC, forced vital capacity; ILD, interstitial lung disease; IPAF, interstitial pneumonia with autoimmune features; P(A)H, pulmonary (arterial) hypertension; SSA, anti-Ro; SSB, anti-La
MDD, multidisciplinary discussion; NSIP, non-specific interstitial pneumonia; OP, organizing pneumonia; RHC, right heart catheterization; TTE, transthoracic echocardiography; UIP, usual interstitial pneumonia; 6MWD, 6-minute walk distance

Table 2. Pharmacological treatment before and after the joint consultation.

Number of patients, %	Before consultation	After consultation
Any immunosuppressive (IS) treatment	83 (49%)	105 (62%)
Initiation of new IS medication		27 (16%)
Stopping of any IS medication		14 (8%)
Change in any IS treatment dose		20 (12%)
Corticosteroids (any dose)	57 (34%)	74 (44%)
Mycophenolate mofetil	19 (11%)	29 (17%)
Azathioprine	3 (2%)	4 (2%)
Methotrexate	7 (4%)	10 (6%)
Cyclophosphamide	1 (1%)	1 (1%)
Rituximab	12 (7%)	19 (11%)
Tocilizumab	3 (2%)	9 (5%)
Other	17 (10%)	21 (12%)
Double immunosuppressive treatment[†]	32 (19%)	48 (28%)
Triple immunosuppressive treatment[†]	2 (1%)	7 (4%)
Antifibrotic treatment (nintedanib)	4 (2%)	18 (11%)
Combination immunosuppressive & antifibrotic treatment	3 (2%)	13 (8%)
No specific treatment	86 (51%)	60 (35%)

[†]includes corticosteroids in any dose

FIGURES

Figure 1. Patient journey and referral to the interdisciplinary consultation pulmonology-rheumatology.

Figure 2. Interdisciplinary diagnosis and management of patients with suspected ILD and/or CTD.

† The choice of the immunosuppressive treatment depends on the specific CTD-ILD, extrapulmonary manifestations and the estimated individual risk-benefit ratio of the treatment. The addition of antifibrotic treatment depends on the ILD progression, the CT scan pattern and the estimated individual risk-benefit ratio of the treatment.

‡Screening for cancer and is indicated in CTDs and risk factors that are highly associated with malignancy, including Sjögren's Syndrome, SSc, and IIM.[28,29]

Abbreviations: aHSCT, autologous haematopoietic stem cell transplantation; BAL, bronchoalveolar lavage; CTD, connective tissue disease; EBUS-TBNA, endobronchial ultrasound-guided transbronchial needle aspiration; ILD, interstitial lung disease; LTX, lung transplantation; MDD, multidisciplinary team discussion; MRI, magnetic resonance imaging; TBCB, transbronchial cryobiopsy

Figure 3. Extrapulmonary signs of CTD in a patient with anti-Jo-1 positive Antisynthetase Syndrome.

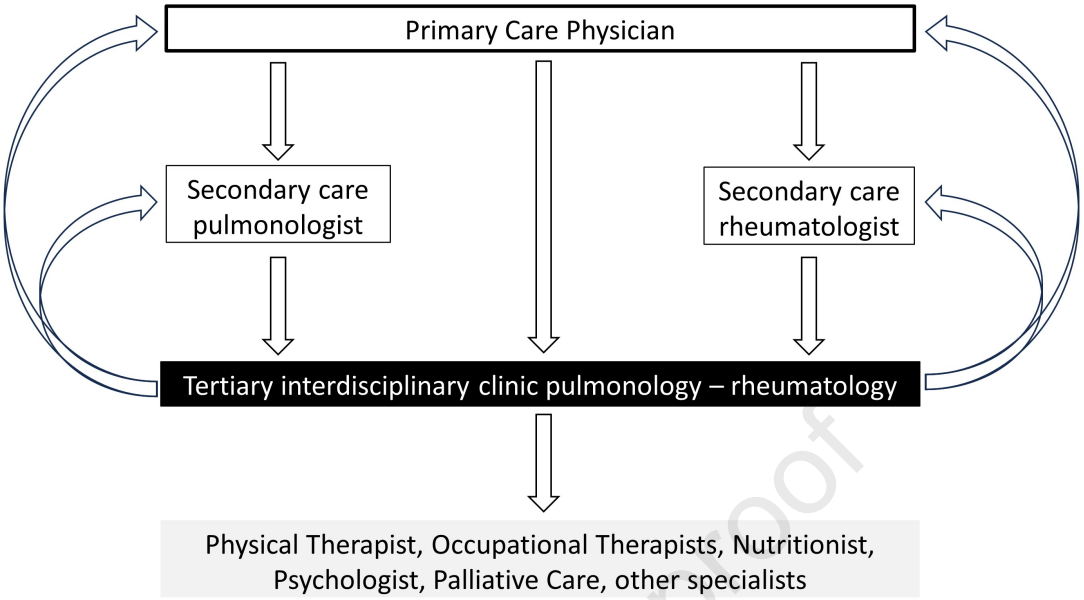
The 67-years old man reported a gradual loss of muscle strength that bothered him most when lifting the arms, progressive exertional dyspnea, and low-grade fever over several weeks prior

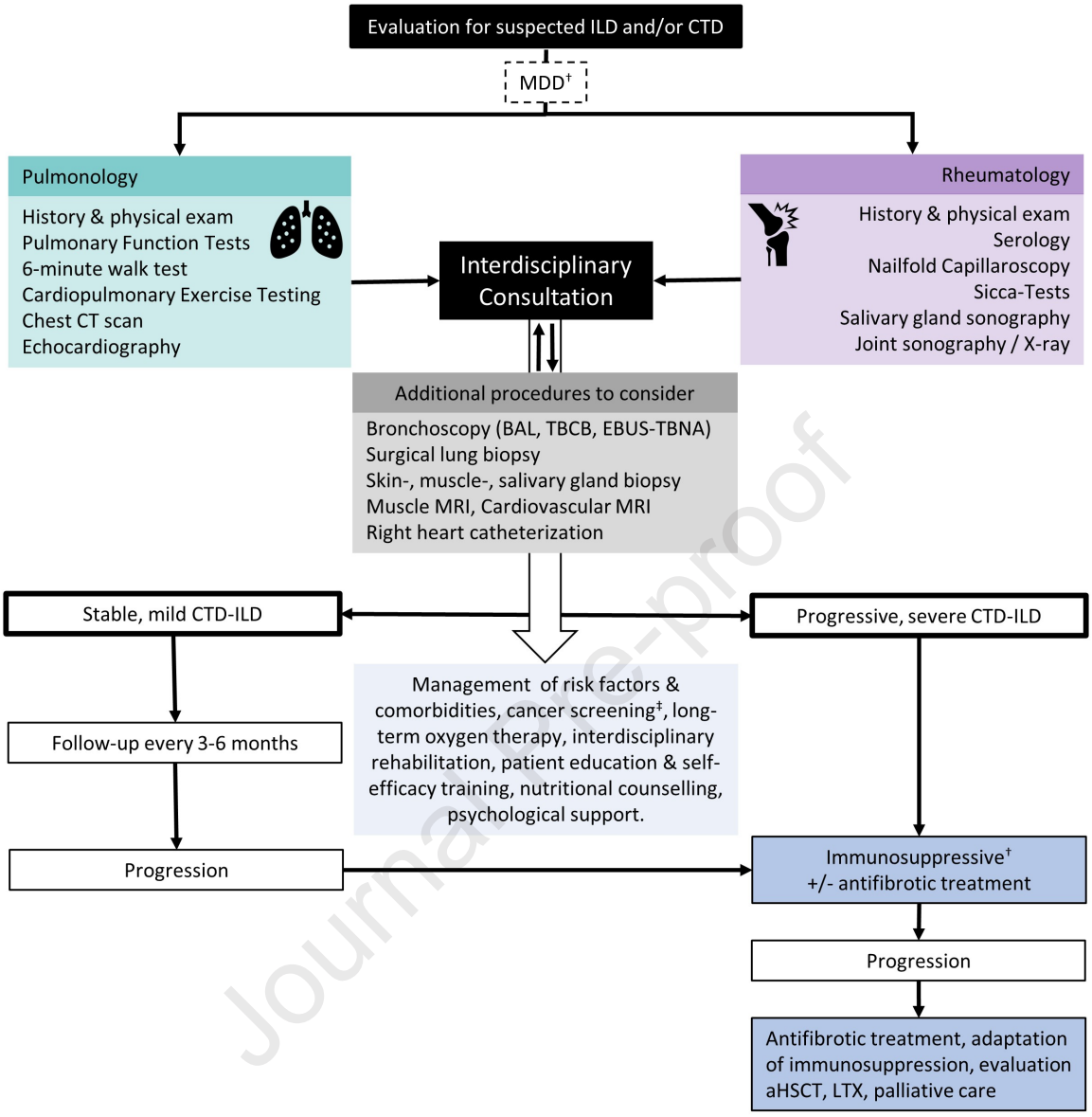
to presentation. A-B) Characteristic *mechanic's hands* with hyperkeratosis and fissures on the hands, especially on the palmar lateral side of the fingers. C) Positive HEP2 cytoplasm (AC 20 pattern, https://www.anapatterns.org/; cytoplasmic fine speckled) was matched by positivity for anti-Jo-1 antibody with additional detection of anti-SS-A (Ro-52, TRIM 21) while the antinuclear pattern (ANA) was speckled. Furthermore, creatine kinase (CK), aspartate transaminase and alanine transaminase were elevated. Due to the elevation of CK-MB, troponin T and I as well as pericardial effusion on chest CT cardiac MRI was performed (D): T1 mapping without ischemic myocardial scars. Diffusely increased T1 time (➤, white areas within the myocardium), increased extracellular volume fraction indicating diffuse myocardial fibrosis, and increased T2 time indicating myocardial oedema typical for myocardial involvement in the context of antisynthetase syndrome. Native T1-mapping (septal): 1321ms (norm 3T:1021-1240ms), ECV: 31% (norm: 25 ± 4%) T2-mapping (septal): 46ms, individual areas with up to 53ms, e.g. inferoseptal basal (norm 3T: 31-47ms). Clear signs of inflammatory muscle involvement and disease activity (muscle fiber necrosis, inflammation, denervation, →) were present in all muscles of the lower extremities and pelvic girdle (E, F).

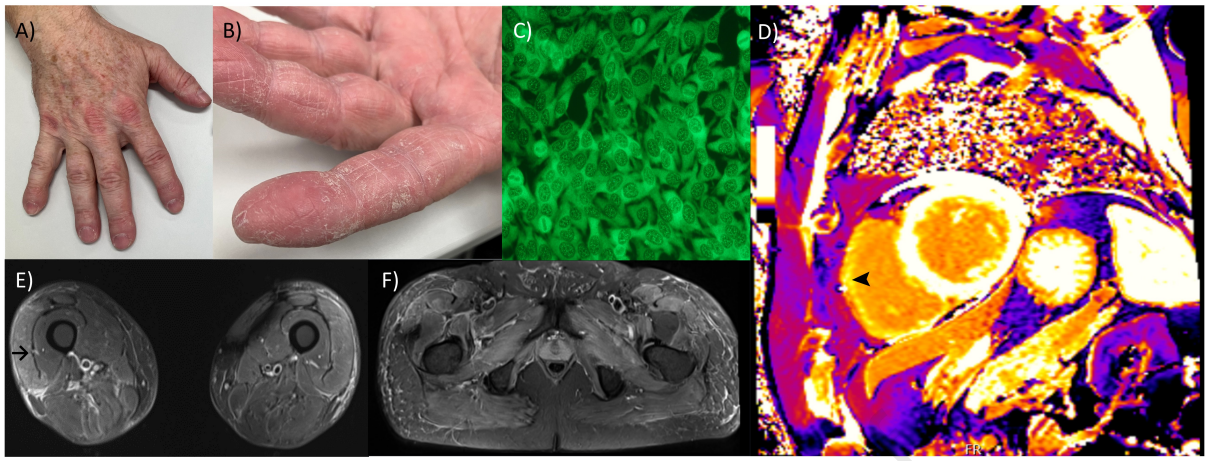
Figure 4. Evolution of CTD-ILD on chest CT scan in a patient with anti-Jo1 positive Antisynthetase Syndrome.

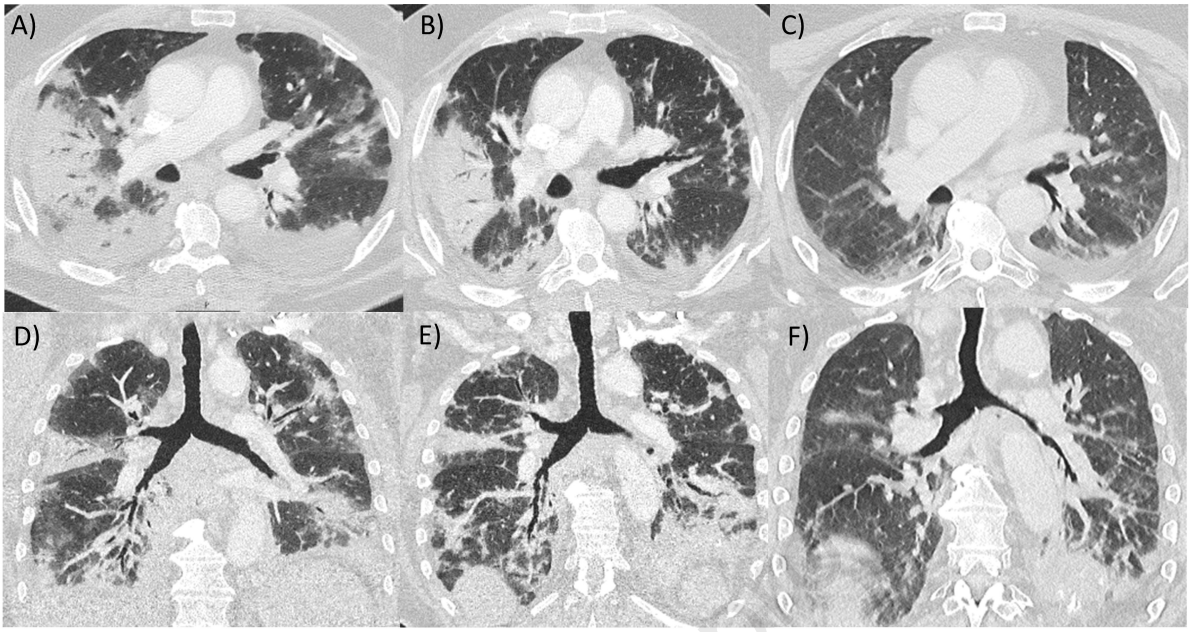
Axial (A-C) and corresponding coronal (D-F) chest CT scan images from a 67-years old man with anti-Jo-1 positive antisynthetase syndrome. At first presentation (A, D) there are patchy ground glass opacities and consolidations with bronchopneumograms in all lung sections, well compatible with organizing pneumonia. At acute presentation cyclophosphamide 1200mg i.v. and high-dose methylprednisolone i.v. were administered, with tapering of

prednisone over the following weeks (1000mg per day for 3 days, 125mg per day for 4 days, 80mg per day for 2 weeks). Two weeks from initial presentation (B, E) radiological findings were regressive, and oxygenation had clearly improved. Three weeks and 5 weeks from initial presentation two doses of Rituximab 1000mg were administered, and prednisone carefully tapered. Two months from first presentation (C, F) there was a clear decrease in consolidations. Dyspnea had improved, but pulmonary function tests showed a persistent restrictive physiology (forced vital capacity [FVC] 61% predicted, diffusing capacity for CO [DLCO] 64% predicted). Due to worsening of myalgias and increase in creatine kinase intravenous immunoglobulin (2g per kg bodyweight) was administered with good clinical response. Five months from initial presentation FVC had improved to 75% predicted, DLCO to 81% predicted, and 6-minute walk distance by 100m to 537m (94% predicted).









Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: