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Case Report

Asymptomatic and slowly progressive anti-MDA5 ILD: A report of three cases deviating from a notoriously rapidly progressive ILD☆

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ABSTRACT

Background: Anti-melanoma differentiation-associated gene 5-positive (anti-MDA5) dermatomyositis (DM) is a rare autoimmune disease associated with rapidly-progressive interstitial lung disease (RP-ILD.) The reported morbidity and 6-month mortality remains high from 33 to 66 % with RP-ILD most often developing within three months of diagnosis. Most cases require aggressive immunosuppression with combination therapy. Asymptomatic or slowly progressive cases of anti-MDA5 ILD are not well described in the literature. We report three cases of Latino patients with asymptomatic or slowly progressive anti-MDA5 ILD.

Case descriptions:

Case 1: A 54-year-old woman from Honduras with known diagnosis of anti-MDA5 dermatomyositis presented for ILD. She denied respiratory symptoms. Computed tomography (CT) chest showed multifocal patchy areas of scattered groundglass opacities throughout all lobes of the lungs, predominately in a subpleural distribution within the lower lobes. Pulmonary function testing (PFTs) showed mild-to-moderate restriction. She was treated with mycophenolate mofetil monotherapy for her skin manifestations. At 18 months follow-up, she denied respiratory symptoms, and PFTs were normal.

Case 2: An 80-year-old man from Cuba was seen in pulmonary clinic to establish care. He was diagnosed with pulmonary fibrosis 11 years earlier with positive anti-MDA5. He denied respiratory symptoms. PFTs showed moderate obstruction and mild to moderate restriction. CT chest showed reduced lung volumes and findings compatible with usual interstitial pneumonia. He was started on nintedanib. Fifteen months following the initial visit, his PFTs remained stable. Follow-up CT chest showed stable pulmonary fibrosis. At all subsequent visits, he reported mild to moderate, slowly progressive dyspnea on exertion and was maintained on nintedanib. Thirteen years after his initial ILD diagnosis, he was diagnosed with pancreatic adenocarcinoma.

Case 3: A 70-year-old woman from Peru presented to pulmonary clinic with cough for two months. She also reported pain in several metacarpophalangeal joints. She denied dyspnea. Rheumatologic serologies revealed positive anti-MDA5. PFTs were normal. Her cough was treated with cough suppressants and resolved. At a subsequent visit 8 months after presentation, she denied respiratory symptoms, and her joint pain remained mild. Given her lack of respiratory symptoms and normal PFTs, she was not initiated on ILD-specific treatment.

☆ This work was performed at: University of Miami.

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Conclusions: While anti-MDA5 ILD is certainly associated with RP-ILD, clinicians should maintain awareness that there may be cases of asymptomatic or slowly progressive ILD as well.

Abbreviations

Anti-MDA5	anti-melanoma differentiation-associated gene 5
RP-ILD	rapidly progressive interstitial lung disease
CXR	chest x-ray
CT	computed tomography
DLCO	diffusing capacity for carbon monoxide
FEV1	forced expiratory volume in the first second
FVC	forced vital capacity
GGO	ground-glass opacities
ILD	interstitial lung disease
mMRC	modified medical research council
UIP	usual interstitial pneumonia
f-NSIP	fibrotic non-specific interstitial pneumonia
OP	organizing pneumonia
LLN	lower limit of normal
PPF	progressive pulmonary fibrosis
DM	dermatomyositis

1. Introduction

Anti-melanoma differentiation-associated gene 5-positive (anti-MDA5) dermatomyositis (DM) is a rare autoimmune disease associated with rapidly progressive interstitial lung disease (RP-ILD.) The majority of patients with anti-MDA5 DM are clinically amyopathic (CADM) and at higher risk for ILD compared to other DM phenotypes [1]. Anti-MDA5 DM ILD has been described with higher prevalence in Japanese and Chinese patients with female predominance in the 6th decade of life [2]. Patients may experience rapidly progressive disease ILD despite aggressive immunosuppressive treatment, often requiring aggressive, combination immunosuppressing therapy [3]. Despite increasing awareness and aggressive treatment, the reported morbidity and 6-month mortality remains high from 33 to 66 % with RP-ILD most often developing within three months of diagnosis [2]. Various scoring systems have been proposed to identify indicators for development of RP-ILD in anti-MDA5 patients in cohorts of patients with acute and chronic ILD [4,5]. However, asymptomatic or slowly progressive cases of anti-MDA5 ILD are not well described in the literature [6]. We report three cases of Latino patients with asymptomatic or slowly progressive anti-MDA5 ILD (Table 1, Fig. 1).

2. Case 1

A 54-year-old woman, originally from Honduras, presented to dermatology for evaluation of skin rash with erythroderma (Fig. 2). She was evaluated with laboratory testing and skin biopsy. Labs were notable for anti-MDA-5 positivity. A skin biopsy was consistent with dermatomyositis. She denied respiratory symptoms. While she did report mild arthralgias, creatinine kinase (CK) and examination were not consistent with muscle involvement. She was initiated on treatment with hydroxychloroquine.

Twelve months after her initial presentation, she developed worsening skin rash and pruritis prompting hospitalization. She was treated with intravenous methylprednisolone 100 mg daily for three days and initiated on mycophenolate mofetil up titrated to 1000 mg twice per day. She was discharged home with a prednisone taper. During her hospitalization, a CT chest was performed and showed multifocal patchy areas of ground glass opacities (GGO) affecting all lung lobes with predominantly lower lobe distribution without fibrotic features. She denied respiratory symptoms at the time of hospitalization with exception of mild dyspnea with walking up inclines or stairs which she reported had been long-standing and stable.

Upon evaluation in ILD clinic after discharge, she continued to endorse minimal dyspnea on exertion modified Medical Research Council (mMRC) grade 0 to 1. Her pulmonary function testing (PFTs) showed mild restriction with forced vital capacity that improved and normalized over the following 18 months of available data. A follow-up CT scan performed 18 months from initial evaluation was unchanged and notably without any concern of progression (Image Series 1). Given her minimal respiratory symptoms, improving PFTs, and mild, stable CT findings, she was maintained on the mycophenolate mofetil as prescribed for the skin involvement. A lung biopsy was not performed because it was felt unlikely to change management.

In subsequent visits with dermatology and rheumatology, her skin involvement was well controlled on mycophenolate monotherapy. She did not develop muscle involvement. She was found to have a positive Sjogren's antibody (SS-A) but denied other clinical

Table 1
Patient demographics.

	Case 1	Case 2	Case 3
Age at diagnosis	54	69	70
Sex	Female	Male	Female
Smoking history, pack/years	Never	Former, 90 pack/year	Former, <10 pack/year
Birth country	Honduras	Cuba	Peru
History of asthma/COPD	No	No	No
Other medical conditions	Hypertension	Anemia due to B12 deficiency, hypertension, basal cell carcinoma, pancreatic adenocarcinoma	Coronary artery disease
Family history of autoimmune disease	None	None	None
Exposure history	-Cooking with wood burning stoves	-Pet Senegal parrot in home, 2 years prior -Regular outdoor pigeon feeding -Feather pillows	-No known exposures

Description: table describing demographics of the three patient cases described.

symptoms of Sjogren's disease.

She was found to have a mass suspicious for malignancy on her left neck approximately 18 months from initial diagnosis; she has refused to proceed with biopsy and additional neck imaging was pending at the time of publication.

3. Case 2

A 69-year-old man from Cuba was referred to pulmonary clinic for abnormal chest x-ray (CXR). He denied respiratory symptoms at the time of presentation (Fig. 3). The rationale for initial CXR was unclear given his lack of symptoms. Clinical history was notable for one year exposure to a Senegal parrot in his home two years prior and exposure to outdoor pigeon feeding on a regular basis. He was also noted to have exposure to feather pillows in his home. His initial CT scan was reported to have bilateral, lower lobe predominant interstitial changes with evidence of fibrosis; there was concern for mosaicism and air trapping. Serologies were notable for positive anti-double stranded DNA, anti-MDA-5, and hypersensitivity panel. He underwent surgical lung biopsy with pathology reported as usual interstitial pneumonia with lymphoid hyperplasia and very rare multinucleated giant cells. The surgical lung biopsies were reviewed at two academic centers with ILD expertise. With multidisciplinary collaboration, the leading consideration was usual interstitial pneumonia which was favored over chronic hypersensitivity pneumonitis. He did not display other clinical signs of connective tissue disease. He was counselled on avoidance of antigen exposures. He was treated with n-acetylcysteine.

He continued to deny respiratory symptoms with mMRC grade 0 dyspnea for the subsequent nine years. PFTs performed two years after initial diagnosis were normal. He eventually began to develop progressive respiratory symptoms approximately nine years after

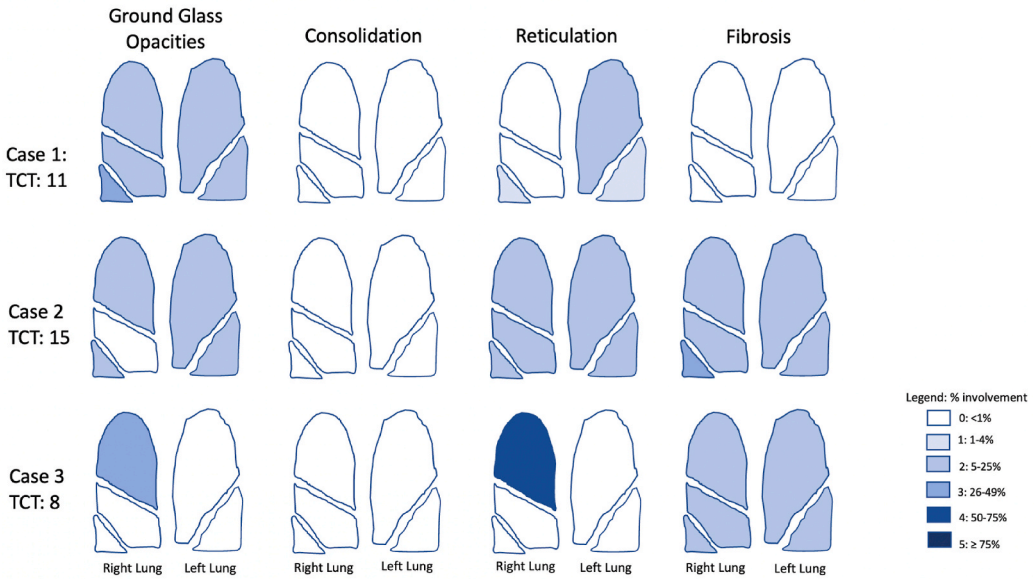

Fig. 1. CT imaging findings using a scoring system.
Description: Representation of radiologic findings using a scoring system to describe tissue involvement.
TCT = Total CT score calculated by summing the individual lobar scores.

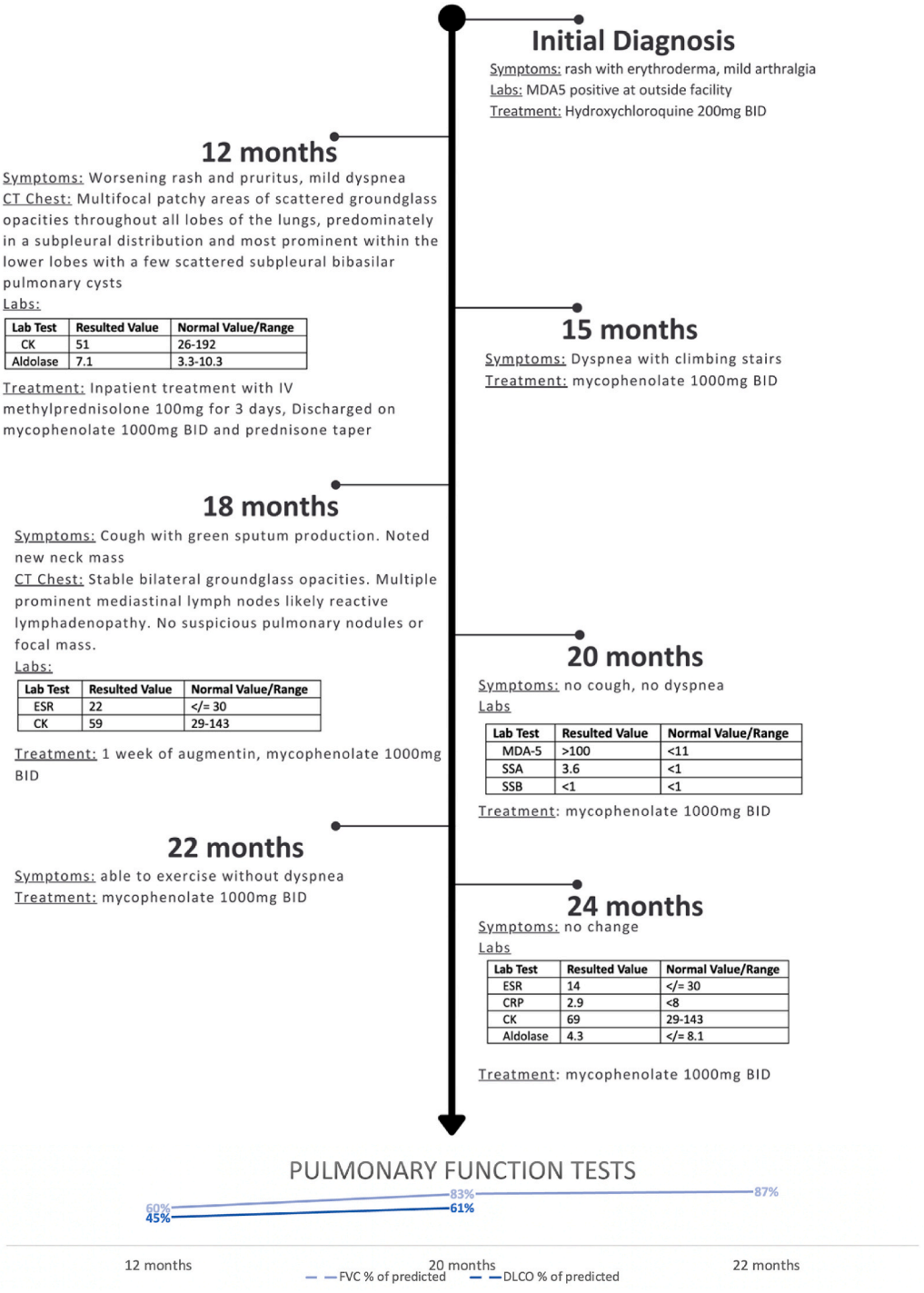

Fig. 2. Case 1 timeline and pulmonary function Testing.
Description: Timeline of clinical course for case 1 with depiction of pulmonary function testing over time.

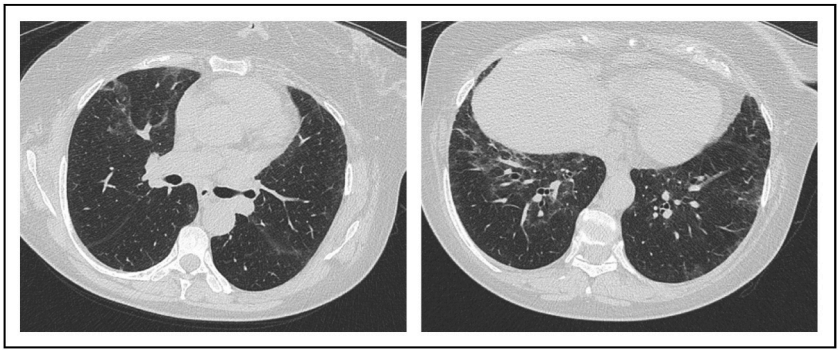

Image Series 1. CT key images from case 1 at 18 Months.
Stable bilateral groundglass opacities. No suspicious pulmonary nodules or focal mass.
Description: Key image series of CT imaging from case 1 at 18 months from diagnosis.

diagnosis, with mMRC grade 2 dyspnea. His PFTs showed decline with restrictive physiology twelve years after diagnosis. He also developed chronic hypoxemic respiratory failure requiring continuous oxygen supplementation of 2 L via nasal cannula. Subsequent CT scans showed progression of fibrotic changes and waxing and pulmonary nodules requiring monitoring. He was started on nintedanib twelve years after diagnosis and n-acetylcysteine was discontinued. A skin biopsy performed twelve years after diagnosis for mild rash was negative for dermatomyositis. He did not develop other clinical symptoms consistent with connective tissues disease. At 12 years and 5 months, his CT chest showed extensive paraseptal bullous changes and bilateral fibrotic interstitial changes with interlobular septal thickening.

During his course, he intermittently developed pulmonary nodules which were monitored with serial CT scans. Thirteen years after his initial ILD diagnosis, CT scan showed stable pulmonary fibrosis with fluctuating lung nodules with recommended short term follow-up imaging (Image Series 2). At that time, he was experiencing worsening unintended weight loss prompting further evaluation which revealed a pancreatic mass. Biopsy confirmed pancreatic adenocarcinoma. Addition PET CT imaging showed concern for metastatic disease to the liver and lung nodules. He was initiated on palliative chemotherapy and died due to complications of pancreatic cancer 14 years after initial ILD diagnosis.

4. Case 3

A 70-year-old woman from Peru was referred to pulmonary clinic for dry cough following COVID-19 infection (Fig. 4). She reported symptomatic COVID-19 two months prior to evaluation with fevers, chills, malaise, pleuritic chest discomfort and cough. She was not prescribed steroids or other specific therapies for COVID-19. She underwent CXR which showed concern for ILD

Upon evaluation in pulmonary clinic two months later, she complained of persistent dry cough since the COVID-19 diagnosis. She also reported pain in several metacarpophalangeal joints. She denied dyspnea. She was further evaluated with rheumatologic serologies which revealed positive anti-MDA-5. PFTs did not show evidence of obstructive of restrictive changes. Her follow-up CT showed interstitial thickening with peripheral left fibrotic changes, most consistent with probable usual interstitial pneumonia (UIP) pattern.

At a subsequent visit 6 months after presentation, she denied respiratory symptoms, mMRC grade 0 dyspnea. She denied myalgias or arthralgias. CT scan was stable from prior but did show a new 6 mm right middle lobe nodule (Image Series 3). She did notably have a pruritic skin rash on her arms with dermatographia. She was referred to dermatology. Repeat pulmonary function testing was performed and normal. Given her lack of symptoms and normal pulmonary function testing, invasive diagnostic testing was not pursued. She was monitored without initiation of ILD specific treatment.

5. Discussion

Here we report three patients with asymptomatic or slowly progressive anti-MDA5 DM ILD. All three cases were clinically amyopathic DM, and only one case displayed dermatologic involvement which is consistent with other reports of anti-MDA5 ILD in which pulmonary manifestation is common [2]. Despite the notorious association with RP-ILD usually within months of diagnosis, these three cases did not show progression at the time of our report at twenty four months, nine years and eight months respectively. One case demonstrated progression after nine years from diagnosis over the subsequent four years. Our cases also had minimal exposure to immunomodulating medications with no specific therapy or monotherapy compared to the cases in literature often describing aggressive triple therapy with intravenous treatment and hospitalizations.

When compared to previously reported cases of slowly progressive and stable ILD in patients with anti-MDA5 positivity, our patients have some unique characteristics. First, two of the three patients had relatively low anti-MDA5 levels. One of the three patients had a highly elevated level but remained notably asymptomatic. Second, all three patients had normal CK levels; this is in direct

Initial Diagnosis

Symptoms: no respiratory symptoms
CT Chest: bilateral, lower lobe predominant interstitial changes with evidence of fibrosis. Concern for mosaicism and air trapping.
Labs:

Lab Test	Resulted Value
MDA5	positive (unknown value)
SSA/SSB	positive (unknown value)
Hypersensitivity panel	positive

Treatment: n-acetylcysteine

2 months

Symptoms: no respiratory symptoms

9 years

Symptoms: Progressive dyspnea, mMRC grade 2

12 years

Symptoms: dyspnea
CT Chest: showed progression of fibrotic changes and waxing and pulmonary nodules
Labs:

Lab Test	Resulted Value	Normal Value/Range
ESR	16	0-10
CRP	<0.1	0.0-0.5
CK	35	39-308
Aldolase	2.6	3.3-10.3
MDA5	30	<11
SSA/SSB	negative	
Hypersensitivity panel	negative	

Treatment: 2L supplemental oxygen, nintedanib

12 years, 5 months

Symptoms: stable dyspnea
CT Chest: Extensive paraseptal bullous changes are seen in both lungs. No definitive masses or consolidations are seen. Scar tissue formations are present in both sides and throughout the lungs with the significant thickening of the interlobular septa
Treatment: 3L supplemental oxygen at rest, 4L with exertion, nintedanib

13 years, 1 month

Symptoms: stable dyspnea, new pancreatic lesion, 30lb weight loss
CT Chest: Pulmonary fibrosis, similar to prior study. No nodular densities in the lungs as described, while other nodules have resolved since prior study.
Treatment: 3L supplemental oxygen, nintedanib

13 years, 3 months

Symptoms/interval history: stable dyspnea, new diagnosis of pancreatic adenocarcinoma
Treatment: 3L supplemental oxygen, nintedanib

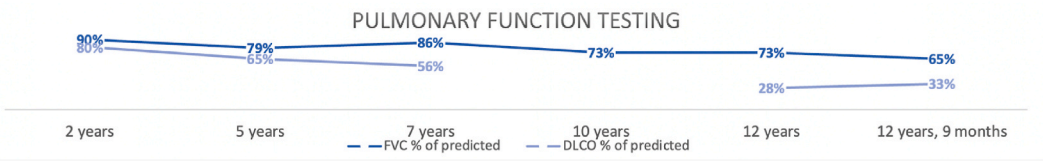

Fig. 3. Case 2 timeline and pulmonary function Testing.
Description: Timeline of clinical course for case 2 with depiction of pulmonary function testing over time.

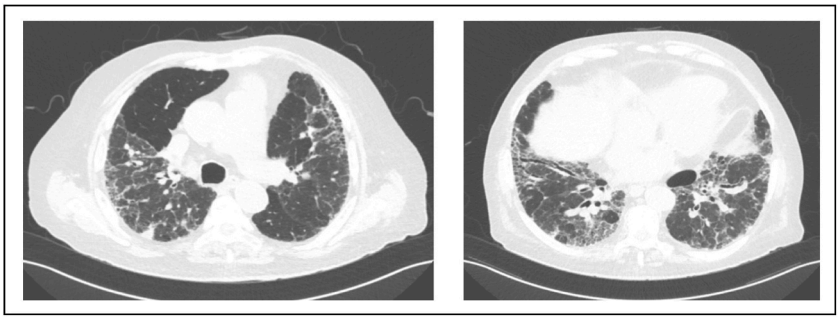

Image Series 2. CT Key Images from Case 2 at 13 years and 1 month.
Pulmonary fibrosis, similar to prior study. No nodular densities in the lungs as described, while other nodules have resolved since prior study.
Description: Key image series of CT imaging from case 2 at 13 years and 1 month from diagnosis.

contrast to the cases reported by Allenbach et al. and where patients with more favorable prognosis also had increased CK [7]. Additionally, one of the asymptomatic patients had a positive SSA antibody contrary to reports that Ro-52 elevation association with worse prognosis in ILD in these patients [8]. Finally, previously reported cases have largely described patients of East Asian descent. Our cohort of patients from Latin America is unique amongst existing reports.

Our three cases showed variable imaging patterns on CT scan. Case 1 demonstrated diffuse bilateral GGOs and reticulation without fibrosis. Cases 2 and 3 had ground glass changes as well as reticulation and fibrosis. We utilized a scoring system to summarize the extent of GGO, reticulation, consolidation, and fibrosis for each as shown in Fig. 1. A total CT score was calculated revealing 30–60 % of total lung involvement consistent with stable mild to moderate ILD significantly deviating from the described cases of MDA5 RP-ILD.

There are many possible explanations of why these patients did not experience a rapidly progressive or severe chronic ILD. While the pathophysiology of anti-MDA5 ILD is not well understood, genetic or environmental differences in these patients with Hispanic or Latino background may play a role [9]. Two of these patients had confirmed or suspected malignancy. The association of malignancy reported in patients with known anti-MDA5-ILD is low with less than 5 % incidence reported [10]. However, the incidence may be underestimated given the high morbidity and mortality rate typically noted from respiratory failure in these patients prior to detection of malignancy. In these patients, routine oncologic screening is recommended with additional screening based on individualized risk factors. Increased availability of laboratory testing of anti-MDA5 and increased utilization of CT scans could also contribute to detection of these cases which could have otherwise been missed.

Our cases highlight common diagnostic challenges in these cases and the need for multidisciplinary input. The classification and diagnostic criteria for CADM have been evolving with reports estimating that up to 25 % of patients may be missed pending which criteria are utilized [11]. We acknowledge that these patients may not represent classic anti-MDA5 ILD by classification criteria nor full criteria as interstitial pneumonia with autoimmune features (IPAF), however clinicians should not ignore the serologic findings in these patients with imaging evidence of ILD given the known risks of RP-ILD [11]. While lung biopsy may assist with diagnosis, the risks of invasive testing was deferred in cases 1 and 3 due to minimal symptoms and stability. The biopsy in case 2 showed UIP with atypical features still requiring diligent, multidisciplinary correlation.

There are not currently clear guidelines for the management of patients with anti-MDA5 positivity. Diligent surveillance is required given the risk of developing RP-ILD. Close monitoring for clinical symptoms and PFTs can be considered every 3 months to establish a trajectory. We suggest obtaining a CT with any change in PFTs or symptoms. As dermatologic or musculoskeletal symptoms arise, multidisciplinary input from rheumatology and dermatology are warranted to optimize medical management and clinical correlation.

6. Conclusion

In summary, while anti-MDA5 ILD is certainly associated with RP-ILD, clinicians should maintain awareness that there may be cases of asymptomatic or slowly progressive ILD as well. Clinical acumen and close monitoring remain of utmost importance in patients with anti-MDA5 ILD. Further study of this patient population is required to understand the pathophysiology and develop effective risk models and treatment strategies.

7. Learning points

- Anti-MDA5 ILD can have a more slowly progressive course and does not always present as rapidly progressive ILD
- With cautious monitoring, patients with anti-MDA5 ILD may not require aggressive multidrug therapy
- There is a need for further research on race or ethnicity based clinical phenotypes in Anti-MDA5 ILD
- There is a need for further research on cancer incidence among CADM based on phenotype of disease, (i.e., healthy survivors)

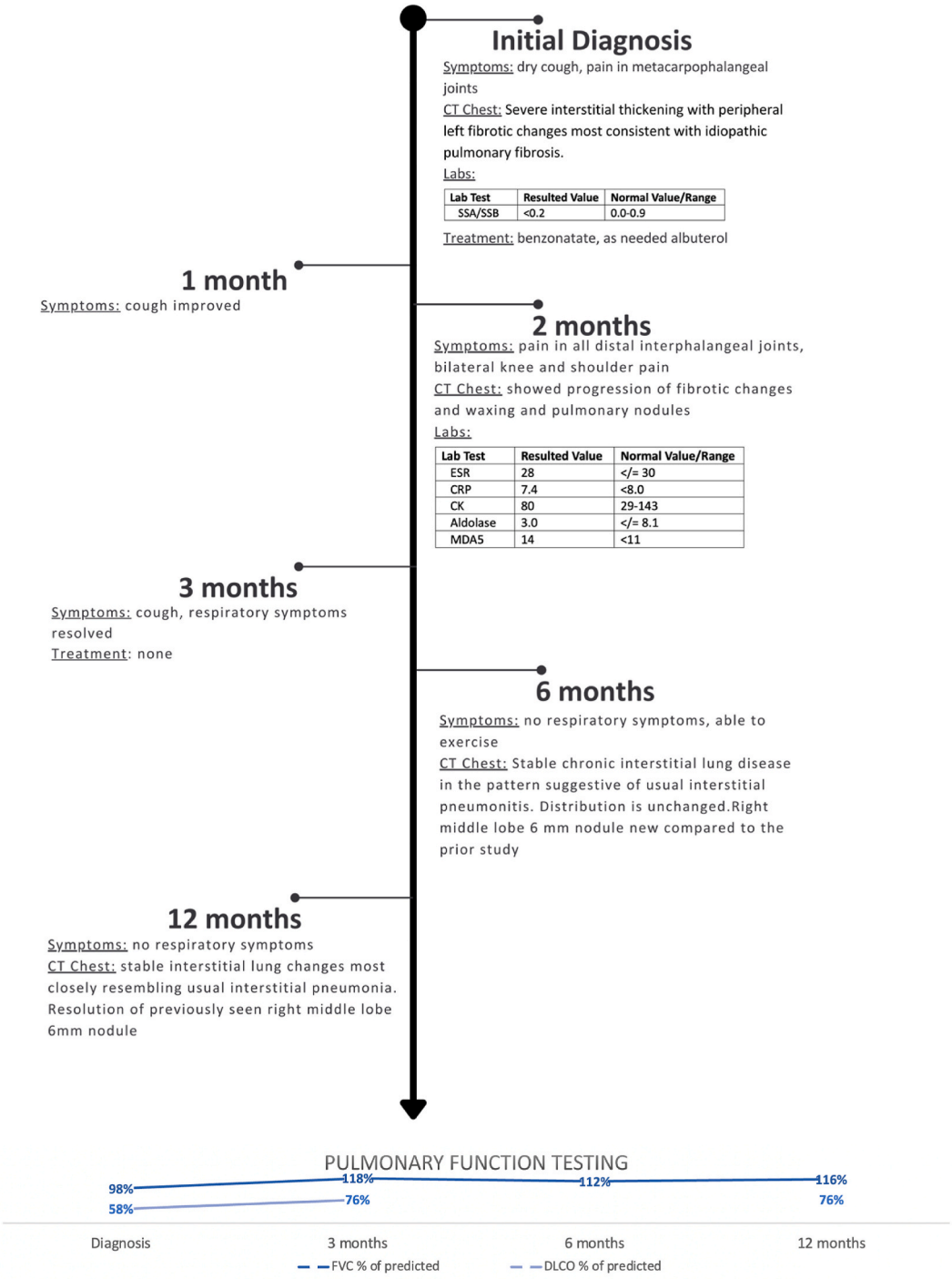

Fig. 4. Case 3 timeline and pulmonary function Testing.
Description: Timeline of clinical course for case 3 with depiction of pulmonary function testing over time.

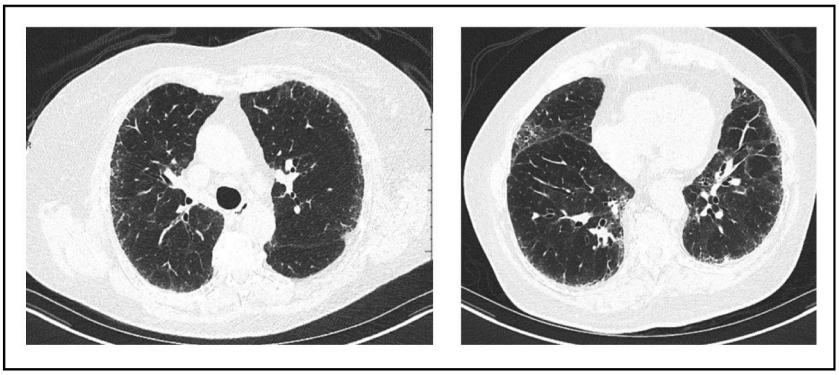

Image Series 3. CT key images from case 3 at 6 Months.
Stable chronic interstitial lung disease in the pattern suggestive of usual interstitial pneumonitis. Distribution is unchanged.
Description: Key image series of CT imaging from case 3 at 6 months from diagnosis.

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None.

CRediT authorship contribution statement

Rose M. Puthumana: Writing – review & editing, Writing – original draft, Visualization, Data curation, Conceptualization. **Abigail L. Koch:** Writing – review & editing, Supervision, Data curation. **Christopher Schettino:** Writing – review & editing, Visualization, Data curation. **Susan J. Vehar:** Writing – review & editing, Visualization, Supervision, Data curation, Conceptualization.

Declaration of competing interest

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.

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