Rheumatology International (2019) 39:1971–1981
https://doi.org/10.1007/s00296-019-04398-2

Rheumatology
INTERNATIONAL

CASE BASED REVIEW

Clinical spectrum and therapeutics in Canadian patients with anti-melanoma differentiation-associated gene 5 (MDA5)-positive dermatomyositis: a case-based review

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Received: 22 April 2019 / Accepted: 26 July 2019 / Published online: 2 August 2019

Abstract

The objective of the study was to determine the clinical features and treatment course in Canadian patients with dermatomyositis (DM) associated with the anti-melanoma differentiation-associated gene 5 antibody (MDA5). A retrospective chart review of consecutive patients with anti-MDA5 antibody DM from two Canadian tertiary care centre between 2014 and 2018 was done. Twenty-one consecutive cases of anti-MDA5-positive DM were identified. Median age at diagnosis was 52 years, 71% Asians, predominantly Chinese, and 29% Caucasians. In this case series, all patients had either typical DM rash, or vasculopathy and ulceration unique to anti-MDA5-positive DM. 38% of the patients had rapid progressive (RP)-interstitial lung disease (RP-ILD), 33% had chronic ILD and 29% had asymptomatic ILD. Anti-Ro52 positivity was more prevalent in RP-ILD. Mortality was high in the RP-ILD group, with five deaths in eight patients. Lung transplant was life-saving intervention for three of the RP-ILD patients who survived. A review of the literature in treating RP-ILD associated with anti-MDA5 is presented. Although evidence is limited to small case series, cyclophosphamide (CYC) for refractory skin lesions, and CYC or mycophenolate mofetil plus a calcineurin inhibitor or rituximab (RTX) for RP-ILD appear efficacious. This is the largest North American case series of anti-MDA5-positive DM patients to date. There is a wide spectrum of clinical presentation of this entity. Survival is poor in those with RP-ILD; early aggressive immunosuppression and timely lung transplant were life-saving in our patients with RP-ILD.

Keywords Melanoma differentiation-associated protein 5 · Interstitial lung disease · Amyopathic dermatomyositis · Lung transplantation

Introduction

Dermatomyositis (DM) is a heterogeneous group of systemic autoimmune rheumatic disorders typically characterized by muscular and extra-muscular manifestations particularly skin and lung of varying severity. Specific myositis-specific autoantibodies (MSAs) are associated with characteristic clinical phenotypes, which may assist in diagnosis, treatment and prognostication of DM and related complications [1].

Melanoma differentiation-associated gene 5 (MDA5), an RNA-specific helicase that functions in recognizing double-stranded RNA viruses [2], has emerged as an important target of DM-specific antibody that is seen in 10–35% of patients with DM [3–5]. Patients with anti-MDA5 antibody are more likely to have clinical amyopathic DM (CADM), a term coined to describe absent or minimal muscle disease in DM, and to have increased risk

This study has been presented as posters in two conferences previously: 1. Huang K, Shojania K, Yeung J, Avina-Zubieta A (2018) Mda5 antibody positive clinical amyopathic dermatomyositis (CADM): A single tertiary centre case series of 13 patients. Annals of the Rheumatic Diseases 77 (Supplement 2):753. http://dx.doi.org.ezproxy.library.ubc.ca/10.1136/annrheumdis-2018-eular.1887. 2. Huang K, Shojania K, Yeung J, Avina-Zubieta A (2018) MDA5 positive clinical amyopathic dermatomyositis (CADM): A single centre case series of 10 patients. Journal of Rheumatology 45 (7):1045. http://dx.doi.org.ezproxy.library.ubc.ca/10.3899/jrheum.180300.

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of interstitial lung disease (ILD), particularly rapid progressive ILD (RP-ILD) [6, 7]. Cutaneous manifestations unique to anti-MDA5-positive DM include skin ulceration, necrosis, palmar papules and digital ischemia, consistent with underlying vasculopathy seen on biopsy [3].

Case series of anti-MDA5-positive DM are reported worldwide, with the largest from Japan and China, and smaller ones from North America and Europe [3–5, 8–12]. Asian patients had higher frequency of anti-MDA5 antibody among CADM patients as well as stronger association with ILD and especially RP-ILD leading to high mortality [4, 5, 10]. Western literature has limited and somewhat conflicting data on anti-MDA5 association with RP-ILD [3, 8, 9, 11, 12]. In this study, we aim to describe the clinical features and therapeutics of 21 patients with anti-MDA5-positive DM from two large Canadian tertiary centres, thereby identifying the spectrum of this disease entity in Canadian patients. We will also review the evidence in treatment of ILD, specifically RP-ILD associated with anti-MDA5.

Materials and methods

Twenty-one consecutive patients with positive anti-MDA5 antibody were identified from January 1, 2014 to September 30, 2018 from Vancouver General Hospital (any department) and Saint Michael's Hospital (Rheumatology department), both of which are tertiary care centers. Follow-up data were collected till December 30, 2018. Data on history, physical findings, and investigations of the 21 patients were collected by a retrospective chart review using a standardized protocol. ILD was defined as radiographic pulmonary fibrosis noted on high-resolution computed tomography (CT). RP-ILD was defined as acute and progressive worsening of dyspnea requiring hospitalization, supplementary oxygen, or subsequent respiratory failure requiring intubation within 3 months of the ILD diagnosis [12]. Typical DM rash is heliotrope, Gottron's, Shawl and Holster signs.

Total 18 antigens were tested in the Line immunoassay (http://Mitogen.ca, Euroimmun GmbH, Luebeck, Germany). Anti-MDA5 antibodies were measured semi-quantitatively by densitometry: negative, ≤ 10; +, low positive 11–29; ++, moderate positive 30–89; and +++, high positive > 90 units. Serum sample to test anti-MDA5 was usually taken soon after initiation of high-dose corticosteroid but before addition of immunosuppressants.

SAS Enterprise Guide (Version 7.1, Cary, NC, USA) was used for all analyses. Fisher's exact test and non-parametric tests were used for analysis. p value of less than 0.05 is considered statistically significant.

Search strategy

To evaluate the effectiveness of rituximab (RTX) as a treatment for RP-ILD in anti-MDA5 DM patients, we searched MEDLINE, SCOPUS, Web of Science and EMBASE up to June 10, 2019 for English-language sources using the following keywords: MDA5, ILD, and RTX.

In total, 4 articles resulted from MEDLINE, 9 from SCOPUS, 7 from Web of Science and 27 from EMBASE. All articles were reviewed in detail. Review articles, duplicate abstracts, case reports with too little clinical data, and cases using RTX for stable ILD were excluded. A total of 28 articles were included in the final literature review.

Results

Twenty-one consecutive patients with clinical and serological anti-MDA5-positive DM were identified including 17 from VCH and 4 from SMH from January 1, 2014 to September 30, 2018. The clinical characteristics are summarized in Table 1. Overlap myositis antibodies were found in three patients (#2, #7, #20) (see Table 3). All others had MDA5 with or without Ro52 antibodies. The median age at diagnosis was 52 years (range 21–69) with 57.1% females. Median duration from time of onset to the time of diagnosis was 3 months (range 1–14 months). Median follow-up, from diagnosis to either death or end of data collection, was 20 months (range 2–64 months). Our study consisted of predominantly Asians (71.4%) particularly Chinese (52.4%) in origin. There were six Caucasians, representing 28.6% of this cohort. About 57.1% of the patients presented with CADM. Polyarthritis was present in 12 of 21 patients (57.1%). All patients had typical DM rash such as Gottron's sign, heliotrope, V-neck rash and Holster's sign (100%), nine with skin ulceration or vasculopathy (ischemic digits and painful palmar papules), and one patient had panniculitis. All patients had ILD (100%) with RP-ILD in 38.1%, chronic ILD in 33.3% and asymptomatic ILD in 28.6%. Pneumothorax was found in five patients. Among eight patients with RP-ILD, five died and three survived after ECMO bridging to lung transplant. Overall mortality was high at 23.8%. Ro52 antibody positivity was found in 61.9% of this group.

Table 2 illustrates the prevalence of anti-Ro52 in relation to severity of lung or skin disease. Anti-Ro52 was found in 87.5% of RP-ILD, 57.1% of chronic stable ILD and only 33.3% of asymptomatic ILD (NS, p value = 0.12). Similarly, anti-Ro52 was present in 80% of patients with ulcerative skin and refractory vasculopathy versus 36.4% of those without (NS, p value = 0.07). Mortality was 30.8%

Table 1 Summary of demographic, clinical, and laboratory features

	Anti-MDA 5-positive DM ($N=21$)
Age, median (range)	52 (21–69)
Time from onset to diagnosis (months), median (range)	3 (1–14)
Time from diagnosis to death or end of study period (months), median (range)	20 (2–64)
Female, *n* (%)	12 (57.1%)
Caucasian, *n* (%)	6 (28.6%)
Asian, *n* (%)	
Chinese	11 (52.4%)
Filipino	1 (4.76%)
Vietnamese	1 (4.76%)
East Indian	1 (4.76%)
Mixed race (French/Chinese)	1 (4.76%)
Cutaneous manifestations, *n* (%)	
Typical DM rash	21 (100%)
Skin ulceration and refractory vasculopathy	9 (42.9%)
Panniculitis	1 (4.76%)
CADM, *n* (%)	12 (57.1%)
Polyarthritis, *n* (%)	11 (52.4%)
Pneumothorax, *n* (%)	5 (23.8%)
ILD, *n* (%)	21 (100%)
Asymptomatic ILD	6 (28.6%)
Symptomatic and chronic ILD	7 (33.3%)
RP-ILD	8 (38.1%)
Ro52 positivity, *n* (%)	13 (61.9%)

Table 2 Analysis of proportion of patients with Ro52 according to severity of lung or skin disease

	With anti-Ro52, *n* (%)
Severity of ILD	
RP-ILD ($n=8$)	7 (87.5%)
Symptomatic and chronic ILD ($n=7$)	4 (57.1%)
Asymptomatic ILD ($n=6$)	2 (33.3%)
Severity of skin manifestation	
Skin ulceration and refractory vasculopathy ($n=10$)	8 (80%)
Non-severe rash ($n=11$)	4 (36.4%)

in Ro52 antibody-positive patients, compared to 12.5% in Ro52 negative group (NS, p value = 0.61).

Demographics, time of diagnosis, clinical manifestations, serology, treatment and outcome are summarized in Table 3. For further discussion purpose, patients are grouped by the severity of their lung and skin disease manifestations.

Group 1: patients with RP-ILD

Eight patients in group 1 presented with RP-ILD in the context of newly diagnosed anti-MDA5-positive DM. All had typical DM rash and were clinically amyopathic with respiratory symptom at onset. Five (62.5%) had cutaneous ulcers and palmar papules unique to anti-MDA5. Seven (87.5%) had concomitant positive Ro52 antibody. They all had dense consolidation and organizing pneumonia radiographically on chest CT. In addition to glucocorticoids, they all received aggressive immunosuppression including intravenous immunoglobulin (IVIG), mycophenolate mofetil (MMF), cyclosporin (CsA), cyclophosphamide (CYC) and RTX. All except one were intubated for respiratory support due to progressive hypoxemia. Patient #4 declined intubation despite hypoxemic on 100% high flow O_2. Two of the eight patients developed pneumothorax while on ventilation.

Three received venous–venous extracorporeal membrane oxygenation (vv-ECMO) bridging to double lung transplantation. Time from intubation to vv-ECMO was 2, 34 and 24 days, and time from ECMO to double lung transplant was 28, 2 and 16 days, respectively, for patients #1–3. They survived and remained on combination therapy with MMF and tacrolimus (Tac). Lung transplant was not an option for the other five patients at the time of their presentation, either due to lack of resources, rapid deterioration or poor candidacy for transplant. They passed away from severe hypoxemic respiratory failure.

Group 2: patients with symptomatic and chronic ILD

Symptomatic chronic ILD was found in seven patients in group 2, all of whom were CADM. Although ILD was clinically and radiographically evident in these patients, their respiratory status was stable on immunosuppression and none required oxygen therapy. Radiographically, they were described as fibrotic NSIP with characteristic traction bronchiectasis, ground glass opacification, and subpleural reticulation with varying degree of fibrosis. Three patients had spontaneous pneumothorax, a feature reportedly associated with anti-MDA5 (13). Six (85.7%) had symmetric polyarthritis resembling rheumatoid arthritis. Four of the seven patients (57.1%) had concurrent positive Ro52 antibody. Patient #11, a 31-year-old man of Chinese origin, had severe ulcerative cutaneous rash and moderate ILD on CT and pulmonary function test. Glucocorticoid and IVIG were ineffective and he could not tolerate MMF (cytopenia) or azathioprine (AZA) (hepatotoxicity). After starting 6 doses of monthly IV CYC at 750 mg/m^2 together with Tac, he had resolution of the ulcerative rash as well as stabilization of his ILD. Patient #13 in this group is a 27-year-old woman of Chinese origin with refractory ulcerative skin lesions and progressive ILD who only partially responded to IVIG, AZA

Table 3 Description of clinical features, serologies, treatment and outcome of the 21 patients

Case #	Age/sex/race	MM/YY Diagnosis	Cutaneous	MSK	Pulmonary	Serologies	Treatment	Outcome
Group 1: RP-ILD with lung transplant								
1	52M Caucasian	10/2017	Heliotrope, Gottron's, periungual erythema.	Amyopathic	RP-ILD	MDA5 high+ Ro52 high+	GC, CYC, RTX, ECMO/lung Tx and now MMF + Tac	Recurrent pneumosepsis
2	54F Asian-C	06/2017	Heliotrope, Gottron's, cutaneous ulcers	Polyarthritis, Amyopathic	RP-ILD/PTX	MDA5 high+ Ro52+ OJ weak+	GC, IVIG, CYC, RTX x 2 ECMO/lung Tx and now MMF + Tac	Improved and stable
3	59F Caucasian	01/2017	Palmar papules, periungual erythema	Polyarthritis, Amyopathic	RP-ILD/PTX	MDA5 weak+ Ro52+	GC, CYC, ECMO/lung Tx and now MMF + Tac	Improved and stable
Group 1: RP-ILD without lung transplant								
4	43M Asian-V	02/2018	Gottron's, palmar papules, Diffuse violaceous rash, cutaneous ulcers,	Polyarthritis, proximal muscle weakness	RP-ILD	MDA5+ Ro52 high+	GC, CYC, rituximab	Refused intubation and died
5	69M Asian-C	05/2017	Heliotrope, Gottron's	Polyarthritis, hypomyopathic, CK 640	RP-ILD	MDA-5 high+ Ro52+	GC, CYC	Died
6	58F Asian-C	01/2015	Gottron's, mechanic's hands. Skin Bx: DM	Polyarthritis, amyopathic	RP-ILD	MDA-5 high+ Ro52+	MMF X a year. Then GC, CYC, CsA, RTX	Died
7	46F Asian-C	06/2014	Palmar papules, malar/V-neck, Shawl, Holster, mechanic hand, periungual erythema. Skin Bx: DM	Proximal weakness. CK 295.	RP-ILD	MDA5+ (Ro52−) Weakly+ for SRP, TIF1γ, OJ, PL12, PL7 and Ku	GC, IVIG, CYC RTX	Died
8	44F Caucasian	02/2014	Gottron's, ulcerations.	Amyopathic	RP-ILD, PH	MDA5+ Ro52+	GC, MMF and RTX	Died
Group 2: symptomatic chronic ILD								
9	21F-Indian	08/2018	Heliotrope, mechanic's hands	Polyarthritis, AMYOPATHIC	ILD	MDA5+ Ro 52−	GC, AZA, MMF + tac	Relapse on AZA, now stable on MMF + tac
10	65M Asian-C	05/2018	Heliotrope, malar, Gottron's, V-neck, abnormal nail folds, and diffusely erythematous rash with areas of ulceration Skin Bx: DM	Polyarthritis, proximal muscle weakness	ILD	MDA5 weak+ Ro52+	GC, IVIG, IV CYC, Imuran	Relapse in myositis requiring repeat IVIG

Table 3 (continued)

Case #	Age/sex/race	MM/YY Diagnosis	Cutaneous	MSK	Pulmonary	Serologies	Treatment	Outcome
11	31M Asian-C	11/2016	Gottron's and ulcerations. Heliotrope. Skin Bx: DM	Polyarthritis, proximal muscle weakness	ILD	MDA5+ Ro52+	GC, MTX, IVIG, intolerant of MMF and AZA; CYC (6 cycles) +Tac	Stable
12	45M Asian-C	04/2016	Gottron's papules. Shawl's sign. Skin Bx: DM	Hypomyopathic, CK 262	ILD	MDA5 high+ (Ro52−)	GC, AZA	Stable and improving PFT
13	27F Asian-C	02/2016	Heliotrope, Gottron's, cutaneous ulcers, periungual erythema	Polyarthritis, proximal weakness, CK 226	ILD/PTX	MDA5+ Ro52 weak+	GC, AZA, MMF, IVIG, RTX +tac	Persistent rash, recurrent PTX and empyema
14	66M Caucasian	03/2015	Diffuse rash, Gottron's, Heliotrope, periungual erythema,	Polyarthritis, Amyopathic, MRI evidence of myositis	ILD/PTX	MDA5+ (Ro52−)	GC, AZA	Stable
15	59F Asian-F	01/2010	Heliotrope, Gottron's, skin ulcers, periungual erythema. Mechanic's hand	Polyarthritis, Amyopathic	Recurrent PTX, Stable ILD	MDA5+ Ro52+	GC, HCQ, AZA, CsA, and now on MMF and RTX	Stable
Group 3: refractory vasculopathy and asymptomatic ILD								
16	51F Caucasian	07/2017	Periorbital edema, heliotrope, Gottron's, ischemic digits, periungual erythema, palmar papules	CK peaked at 7200	Asymptomatic ILD	MDA5+ Ro 52 weakly+	GC, MTX, AZA, IVIG, MMF, PLEX, IV epoprostenol	MAB infection, slowing improving
17	59M Asian-C	01/2017	Facial rash, skin ulcers, palmar papules	Proximal weakness. CK normal. Muscle Bx: DM	Asymptomatic ILD	MDA5+, Ro52+	GC, IVIG, MMF	Ongoing cutaneous ulcers
18	51F French/Chinese	01/2016	Heliotrope, ulcerative Gottron's, calcifications, periungual erythema, mechanic's hands, panniculitis. Skin Bx: DM.	Amyopathic Biceps muscle Bx: DM	Asymptomatic ILD	MDA5+ (Ro52−)	GC, IVIG, HCQ, AZA, tofacitinib, and completed CYC	Stable
Group 4: controlled skin disease and asymptomatic ILD								
19	44 F Asian-C	03/2016	Shawl and holster sign, palmar papules, periungal erythema	Arthralgia, amyopathic	Asymptomatic ILD	MDA5+ (Ro52−)	GC x 10 month	Inactive disease

Table 3 (continued)

Case #	Age/sex/race	MM/YY Diagnosis	Cutaneous	MSK	Pulmonary	Serologies	Treatment	Outcome
20	69M Caucasian	02/2015	Gottron's, periungal erythema, mechanic's hands, palmar papules	Proximal muscle weakness, CK > 1000, Muscle biopsy DM	Asymptomatic ILD	MDA5+ Ku weak + (Ro52−)	IVIG (April 2015 to now) HCQ, AZA	Inactive disease
21	54F Asian-C	11/2013	Gottron's, periungual erythema, mechanic's hands	Amyopathic	Asymptomatic ILD	MDA5+ (Ro52−)	Prednisone 25 mg × 2 weeks, traditional Chinese medicine	Inactive disease

Typical DM rash is heliotrope, Gottron's, Shawl and Holster signs

C Chinese, *F* Filipino, *V* Vietnamese, *MSK* musculoskeletal, *Bx* biopsy, *CK* creatine kinase, *ILD* interstitial lung disease, *RP-ILD* rapid progressive interstitial lung disease, *PTX* pneumothorax, *GC* glucocorticoid, *MTX* methotrexate, *CsA* cyclosporin, *CYC* cyclophosphamide, *RTX* rituximab, *ECMO* extracorporeal membrane oxygenation, *Tx* transplant, *MMF* mycophenolate, *Tac* tacrolimus, *HCQ* hydroxychloroquine, *AZA* azathioprine, *IVIG* IV immunoglobulin, *PLEX* plasma exchange

and MMF. She finally achieved remission after second dose of RTX and Tac.

Group 3: patients with refractory cutaneous disease and asymptomatic ILD

Three patients in this category have severe refractory cutaneous disease. None had respiratory symptoms initially although both had very mild ILD on chest CT. Radiographically, their chest CT described mild NSIP. Two of three had positive Ro52 antibody. Patient #18 was a 51-year-old woman with moderate ulcerative skin disease which only partially responded to IVIG, hydroxychloroquine (HCQ), AZA and tofacitinib. She subsequently developed extensive biopsy proven panniculitis. Six cycles of monthly IV CYC were instituted with complete resolution of skin manifestations. Patient #16, a 51-year-old Caucasian woman, was diagnosed with breast ductal carcinoma in situ a few months prior to the onset of DM. Subsequent resection of the tumor did not result in improvement of rash. Vasculopathic skin disease progressed despite glucocorticoid, methotrexate (MTX), AZA, MMF and plasma exchange (PLEX). As adjunctive therapy, aspirin, pentoxyphyline, nitroglycerin patch, and calcium channel blockers were tried with no improvement. Due to worsening painful digital ischemia, she received IV epoprostenol infusion which offered moderate short-term benefit. Further escalation to CYC or RTX was limited by mycobacterium abscessus infection in her wrist.

Group 4: patients with well-controlled skin disease and asymptomatic ILD

Patients in this group had well controlled skin disease and asymptomatic ILD only evident on imaging. None of the three patients in this group had concurrent Ro52 antibody. Patient # 19 (a 44-year-old woman of Chinese origin) and patient #21 (a 54-year-old Chinese origin woman) in this group had mild cutaneous rash typical of DM which quickly responded to a brief course of prednisone alone. Neither had any signs of recurrence on long-term follow-up.

Discussion

In this study, we report 21 cases of anti-MDA5-positive DM from two large tertiary centres in Canada, the largest North American case series of this entity to date. The large number of East Asian descent in our cohort of Western world corresponds to the known higher incidence of the disease in this ethnic group and is a unique aspect of our cohort.

In this case series, all had ILD; roughly 1/3 of the patients were asymptomatic with only radiographic evidence, 1/3 symptomatic chronic ILD and 1/3 rapid progressive. The

Table 4 Literature review of 28 cases of anti-MDA5-positive DM with RP-ILD treated with rituximab

References	Age/sex/race	Previous therapy	RTX targeting lesion	Duration prior to RTX	Rx during or after RTX	Outcome
Berianu et al.[a] [25]	7 cases of ILD (4 NSIP, 2 with organizing pneumonia, one UIP)	Unknown	ILD	Unknown	Unknown	One died from RP-ILD. The other 6 stable
Patel et al.[a] [26]	55M African-American	GC, CYC	RP-ILD	Several months	GC, MMF, Tac	Died
Mohammed et al.[a] [27]	44M	None	RP-ILD	Several months	IV GC	Died
Alqatari et al. [28]	49F European	GC	RP-ILD	4 weeks	GC, CYC, IVIG, Tac	Died
So et al. [29]	49F Chinese	MMF, CsA, CYC, IVIg	RP-ILD	18 months	GC	Improved
	50M Chinese	MMF, CYC and Tac	RP-ILD	4 months	GC, Tac	Improved
	38M Chinese	MMF, Tac, IVIg	RP-ILD	21 months	GC	Improved
	48M Chinese	CsA	RP-ILD	18 months	GC	Improved
Ogawa et al. [30]	48M Japanese	GC, CsA, CYC	RP-ILD and skin	125 days	GC, CsA	Improved
Oberg et al.[a] [31]	46M Japanese	Unknown	RP-ILD, necrotizing bronchitis and ulcerative skin lesion	Unknown	GC, CsA	Died
Sultan et al.[a] [32]	23F Hispanic	Unknown	RP-ILD	Unknown	GC, MMF, IVIG, VV-ECMO	Died
Koichi et al. [33]	71F Japanese	GC, Tac, CYC, PMX, IVIG	RP-ILD and skin	102 days	Tac GC	Improved
Tokunaga et al. [34]	71F Japanese	GC, Tac, CsA, CYC	RP-ILD	38 days	GC, CsA, MMF, Tac	Died
	69F Japanese	GC, CsA	RP-ILD	33 days	GC, CsA, IV CYC, Tocilizumab	Died
Watanabe et al. [35]	58F Japanese	GC, Tac, CYC	RP-ILD	3 months	GC, IV CYC, IVIG, PMX	Improved
Hershberger et al.[a] [36]	46F African–American	GC	RP-ILD	Several months	GC, MMF	Improved
Yokochi et al.[a] [37]	61[b] Japanese	GC, CsA, CYC	RP-ILD	21 days	GC, CsA, CYC	Died
	71[b] Japanese	GC, CsA, CYC	RP-ILD	51 days	GC, CsA, CYC	Died
	69[b] Japanese	GC, CsA, CYC	RP-ILD	17 days	GC, CsA, CYC	Died
	75[b] Japanese	GC, CsA, CYC	RP-ILD	21 days	GC, CsA, CYC	Died
Gil et al. [38]	55F Israelis	GC	RP-ILD	N/A	CYC, PLEX	Died
Clottu et al. [39]	68F European	GC, IVIG, CYC, MMF, CsA, Tac (topical), HCQ	Skin	2 year	N/A	Improved

RP-ILD rapid progressive interstitial lung disease, *GC* glucocorticoid, *CsA* cyclosporin, *CYC* cyclophosphamide, *RTX* rituximab, *MMF* mycophenolate, *Tac* tacrolimus, *HCQ* hydroxychloroquine, *IVIG* IV immunoglobulin, *PLEX* plasma exchange, *PMX* polymyxin B-immobilized fiber column

[a]Conference abstract

[b]Unknown gender

clinical spectrum in our patients was very broad, ranging from mild cutaneous disease and asymptomatic ILD requiring minimal treatment, to severe refractory vasculopathic skin disease and fatal RP-ILD. When we compare 15 Asian to 6 Caucasian patients in our series, there was no major signal pointing to more severe disease in one ethnic group, albeit the number is too small to draw definitive conclusions.

Lung transplant for RP-ILD

Three of the eight RP-ILD patients survived after ECMO bridging to lung transplant, which represented the first and largest cases series describing lung transplant as the ultimate life-saving intervention for this entity. Despite maximal immunosuppression and ventilatory support, the other five with RP-ILD who did not receive lung transplant, either due to patient refusal or poor transplant candidacy, died from hypoxemic respiratory failure. High mortality from RP-ILD was also reported in two North American studies [9, 12] and as high as 40–60% within 6 months of presentation in Asian studies [5, 10, 13].

Successful lung transplants in RP-ILD associated with anti-MDA5 were reported in three cases previously. First case was a 52-year-old Japanese female who received a left lower lobe from her daughter and a right lower lobe from her son within 15 days of hospitalization. She remained well on immunosuppression (not specified) [14]. Second case was a 51-year-old Korean man who continued to worsen with treatment including IV CYC, CsA, IVIG and RTX. He went on ECMO for 35 days until double lung transplant on day 48 of hospitalization. He recovered well on MMF and Tac combination therapy postoperatively [15]. Most recently, a report of 38-year-old Caucasian man with anti-MDA5-associated RP-ILD had successful lung transplant after failing glucocorticoid and CYC [16]. Similarly, the three patients in our series who required ECMO would not otherwise have survived without double lung transplant.

Prognostic factors

High positive MDA5 (as opposed to medium or weakly positive) and the presence of anti-Ro52 may carry prognostic values. In our series, RP-ILD was the presentation in 4 of the 5 patients with high positive MDA5, compared to 3 of the 16 patients with medium or weakly positive MDA5, suggesting that perhaps high titer of MDA5 antibody also predicts severe disease. However, one cannot use decreasing MDA5 antibody titer during treatment to predict response because the titer in those who died reduced at the same rate as those who survived [17]. Another potential prognostic marker is Ro52 antibody. There was a propensity of more positive anti-Ro52 with severe ILD observed in our study (Table 2). In the eight patients with RP-ILD, seven (87.5%) had positive anti-Ro52, whereas only four of the seven chronic ILD (57.1%) and two of the six asymptomatic ILD (33.3%) were positive for anti-Ro52. The difference was not statistically significant possibly due to small numbers. This association was also noted in the Barcelona cohort of 14 anti-MDA5 patients [11]. Similarly, although not statistically significant, there was a trend that patients with ulcerative skin or vasculopathy findings were also more likely to have anti-Ro52 (Table 2). Asian patients in general seem to confer a more severe phenotype [4, 5, 10]. Therefore, the discrepancy in prevalence of anti-Ro52 in this case series (62%) compared to other North American cohort (27% in Hall et al. [8]) may be related to much higher proportion of Asian patients in our study.

The exact mechanism as to how anti-Ro52 contributes to a more severe ILD pathology remains unclear. MDA5 functions as an intracellular pattern recognition receptor that recognizes dsRNA viruses and activates type I interferon production. Both MDA5 and Ro52 are highly induced by interferon and perhaps the two may form a novel complex, particularly immunogenic in the innate immune system in response to a viral infection [8]. The association of anti-Ro52 with RP-ILD in patients with anti-MDA5 should alert clinicians for close monitoring.

Treatment of ILD

Treatment approach for myositis-associated ILD was recently proposed in an expert review [18]. Patients with chronic and stable ILD associated with anti-MDA5 were treated the same way as ILD from other connective tissue disease. Glucocorticoid was often required initially. MMF as a steroid sparing agent has been successful in many case studies of ILD associated with anti-MDA5 and was reviewed elsewhere [9]. Emerging evidence also suggests that addition of Tac to either AZA, MMF or CYC in patients ILD associated with myositis enabled significant reduction in prednisone dose, and improved FVC, DLCO and prognosis [19, 20].

Evidence in treatment of RP-ILD associated with anti-MDA5 is scarce and based on case reports only. To date, the best evidence supports either IV CYC with a calcineurin inhibitor (CI) or MMF with Tac [9, 21, 22]. RTX has previously been successfully used in anti-synthetase patients with refractory or severe ILD [23, 24]. For RP-ILD associated with anti-MDA5, we did a literature search for the cases treated with RTX. To date, only 28 cases treated with RTX targeting RP-ILD were reported (Table 4); 15 of the 28 patients responded to RTX. In our study, although RTX was initiated on 6 of the 8 patients with RP-ILD, ECMO bridging to lung transplant was the ultimate life-saving therapy for the 3 patients who survived. For those with symptomatic but stable ILD, RTX was rarely needed for disease control as other conventional therapies appear to be effective.

As clinicians around the world better recognize the clinical presentation of anti-MDA5-positive DM with RP-ILD, early diagnosis and aggressive treatment have been associated with better survival. From previously documented mortality of 40–60% within 6 months of presentation in Asian studies [5, 10, 13] to reported 100% survival in RP-ILD patients when aggressive treatment was instituted early [21],

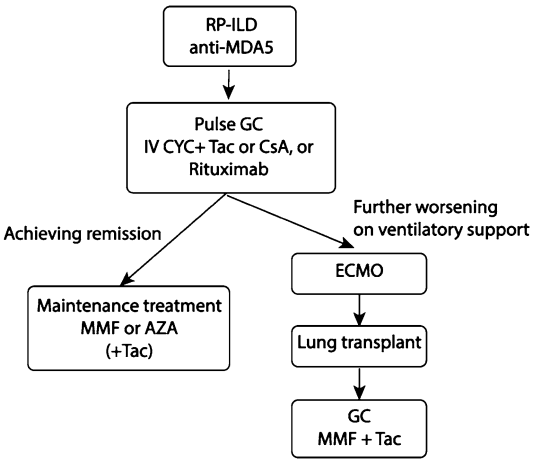

Fig. 1 Proposed treatment algorithm for RP-ILD associated with anti-MDA5 DM. Based on the literature and our own experience, we recommend pulse methylprednisolone with RTX or combined IV CYC with a calcineurin inhibitor as induction therapy. Once remission is achieved, we recommend maintenance therapy with MMF and/or tac. If patients further deteriorate from hypoxia despite mechanical ventilation support, ECMO bridging to lung transplant is likely the only life-saving intervention. Post-transplantation, maintenance therapy would be the same as anti-rejection regimen, a combination of MMF and tac

there is clearly a window of opportunity for these patients with RP-ILD to survive and achieve remission (Fig. 1) with RTX or combined IV CYC with a calcineurin inhibitor as induction therapy [21]. If patients further deteriorate from hypoxia despite mechanical ventilation support, ECMO bridging to lung transplant appears to be the only life-saving intervention in our case series and other reports [14–16]. Based on this evidence, in an appropriate candidate, we recommend consulting transplant team early for assessment.

There are several limitations to this study. First, the patients in this case series may represent more severe disease spectrum due to referral bias, as we only captured patients from two major tertiary centres in Canada. Secondly, there is an overwhelming representation of patients with East Asian descent in this study. Other ethnic groups are underrepresented. Next, we do not have an MDA5 antibody negative control arm in this study. A comparison group is particularly important given the prominent ethnic influence on the patterns of anti-MDA5-positive DM. Lastly, we did not serially measure MDA5 and Ro52 antibody titers throughout treatment to correlate with clinical response, which could be of important prognostic value.

In summary, we report 21 Canadian cases of anti-MDA5-positive DM, the largest North American case series of this entity to date, describing a broad spectrum of clinical presentations of variable severity and new therapeutic options. In the face of continued respiratory deterioration despite ventilatory support, ECMO bridging to lung transplant can be a life-saving intervention.

Acknowledgements We thank Dr. Rohit Aggarwal for critical review of the manuscript, Dr. Hamid Tavakoli for statistical analysis, and Liliana Cartagena for her assistance in ethics approval. We also appreciate Drs. David Collins, Natasha Dehghan and Meghan Hiltz for providing clinical information of the patients included in this study.

Author contributions KH designed the work, acquired the data, performed the analysis, drafted and revised the manuscript, approved the final version, and agreed to be accountable for all aspects of the work. OV acquired the data, revised the manuscript, approved the final version, and agreed to be accountable for all aspects of the work. KS designed the work, acquired the data, revised the draft, approved the final version, and agreed to be accountable for all aspects of the work. JY acquired the data, performed the analysis, revised the draft, approved the final version, and agreed to be accountable for all aspects of the work. RS acquired the data, interpreted the work, revised the manuscript, approved the final version, and agreed to be accountable for all aspects of the work. MN acquired the data, revised the draft, approved the final version, and agreed to be accountable for all aspects of the work. JAA-Z designed the work, performed the analysis, revised the draft, approved the final version, and agreed to be accountable for all aspects of the work. All co-authors are fully responsible for the integrity of the study and the final version of the manuscript.

Funding This study did not receive any funding.

Compliance with ethical standards

Conflict of interest Kun Huang declares that she has no conflict of interest. Ophir Vinik declares that he has no conflict of interest. Kam Shojania declares that he has no conflict of interest. James Yeung declares that he has no conflict of interest. Rachel Shupak declares that she has no conflict of interest. Michael Nimmo declares that he has no conflict of interest. Antonio Avina-Zubieta declares that he has no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This study is approved by research ethics board (REB) at the University of British Columbia (#H18-03216), Vancouver Coastal Health (#V18-03216) and the St Michael's hospital (#18-116). Individual patient's consent is not required by REB.

Informed consent This study is approved by research ethics board (REB) at the University of British Columbia (#H18-03216), Vancouver Coastal Health (#V18-03216) and the St Michael's hospital (#18-116). Individual informed consent was not required by the institution from each individual participant included in the study.

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