Antimelanoma Differentiation-associated Gene 5 Antibody: Expanding the Clinical Spectrum in North American Patients with Dermatomyositis

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ABSTRACT. ***Objective.*** To determine the clinical features associated with the antimelanoma differentiation-associated gene 5 antibody (anti-MDA5) in US patients with clinically amyopathic dermatomyositis (CADM) and classic DM.

Methods. Patients with CADM were consecutively selected from the University of Pittsburgh Myositis Database from 1985 to 2013. CADM was defined by a typical DM rash without objective muscle weakness and no or minimal abnormalities of muscle enzymes, electromyography, or muscle biopsy. DM was defined by Bohan and Peter criteria and was 1:1 matched (sex and age ± 5 yrs) to patients with CADM. Anti-MDA5 autoAb levels were determined using ELISA. Clinical features were compared between CADM and DM and between MDA5-positive and MDA5-negative subjects, using chi-squared and/or Mann-Whitney U tests as appropriate.

Results. We identified 61 patients with CADM who were matched to 61 DM controls (female 62% vs 64%; mean age 44.8 yrs vs 48.2, $p < 0.5$). Anti-MDA5 frequency was the same in both cohorts (13.1%), and anti-MDA5 was significantly associated with a higher likelihood of cutaneous ulcers, digital tip ulcerations, and puffy fingers as well as interstitial lung disease (ILD). Most patients with ILD had rapidly progressive ILD (RPILD) leading to early death. Patients with CADM were more likely to have dysphagia, but there were no other clinical differences seen associated with CADM as compared to classic DM.

Conclusion. Anti-MDA5 positivity had a similar frequency in US patients with CADM and DM and is associated with ILD, RPILD, cutaneous ulcers, digital tip ulceration, and poor survival. (First Release January 15 2017; J Rheumatol 2017;44:319–25; doi:10.3899/jrheum.160682)

Key Indexing Terms:
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The idiopathic inflammatory myopathies (IIM) are a heterogeneous group of systemic autoimmune rheumatic disorders characterized by an immune-mediated attack on skeletal muscle and other organs resulting in muscle weakness and other systemic manifestations. Two major subsets of IIM include dermatomyositis (DM) and polymyositis (PM)[1,2], clinically distinguished by the typical rashes of DM such as Gottron papules and the heliotrope rash. Amyopathic dermatomyositis (ADM) is classically defined as manifesting the hallmark cutaneous features of DM for 6 months or longer without associated proximal muscle weakness, elevated serum muscle enzymes, or abnormalities on other muscle tests such as electromyography (EMG) or muscle biopsy[3,4]. Another subset of DM patients with hypomyopathic dermatomyositis (HDM) with subclinical evidence of muscle involvement but no objective muscle weakness may have mildly elevated muscle enzymes, subtle myopathic EMG, or imaging findings with or without muscle biopsy abnormalities. Hence, clinically amyopathic dermatomyositis or CADM encompasses both ADM and HDM, referring to a subset of DM patients with the pathognomonic rash of DM with or without subtle features of myopathy but with no objective muscle weakness[5,6].

The CADM subset is even more intriguing given the reports from Asian populations noting an increased frequency of interstitial lung disease (ILD) and rapidly progressive ILD (RPILD) in many Japanese and Chinese patients possessing

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Drs. Kuwana and Sato hold a patent on an anti-MDA5 ELISA kit.

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an autoantibody termed anti-CADM-140 [antimelanoma differentiation-associated gene 5 antibody (MDA5)][7,8,9,10,11,12,13]. Apart from these pulmonary features, other clinical features of anti-MDA5+ and anti-MDA5– patients with DM have been found to be similar in Asian patients. The clinical phenotype in MDA5+ US patients from a university-based dermatology clinic noted tender palmar papules and/or skin ulceration[14], while another center noted an increased frequency of mechanic's hands, symmetric polyarthritis (mimicking rheumatoid arthritis), and ILD specifically without RPILD[15]. Conversely, our center reported an increased frequency of both ILD and RPILD in MDA5+ patients[16]. We reported poor survival of anti-MDA5–positive patients in a cohort of 60 patients with CADM and 60 matched patients with classic DM[16]. Using the same cohort, the goal of this study was to determine the unique clinical features seen in CADM and classic DM patients with MDA5 positivity in the United States. We hypothesized that anti-MDA5 positivity in US patients was associated with more severe extramuscular features such as cutaneous ulcers compared to anti-MDA5– patients. We also evaluated the association of ILD, RPILD, and other outcomes with MDA5 titer in both CADM and classic DM subjects.

MATERIALS AND METHODS

We have received ethics board approval from the University of Pittsburgh Institutional Review Board (approval #0409097).

The University of Pittsburgh myositis database includes comprehensive prospectively collected clinical, laboratory, and serologic data with a matching serum repository dating from a period of about 3 decades. Based on strong clinical collaborations involving rheumatology, dermatology, pulmonary medicine, and neurology, most University of Pittsburgh patients are referred to rheumatology and enrolled in our myositis database. Patients with CADM were selected from patients seen from January 1985 to July 2013, with the majority enrolled over the past 20 years. CADM was defined by a typical DM rash without objective muscle weakness for at least 6 months after rash onset and no or minimal abnormalities of serum muscle enzymes (< 3× the upper limit of normal), electromyography, or muscle biopsy (i.e., histologic changes not significant enough to make a conclusive diagnosis). Patients with classic DM were similarly selected and 1:1 matched (sex and age ± 5 yrs) to the patients with CADM. Classic DM included subjects meeting the probable or definite criteria of Bohan and Peter[1,2]. Patients with juvenile DM (JDM) were included in the DM and CADM classification but they were first seen in our myositis center as adults. Myositis autoantibodies were determined by immunoprecipitation as previously described[17,18].

The CADM and classic DM cohorts were further dichotomized as anti-MDA5–positive versus negative, and clinical features and outcomes were assessed using information from the myositis database in combination with the electronic medical record for any missing data. Prospectively collected clinical data on all enrolled patients included pulmonary features of disease (related to ILD, RPILD, and pulmonary hypertension) and all cutaneous manifestations of myositis as well as the various other subjective and objective features of rheumatic disease. ILD was defined as radiographic pulmonary fibrosis noted on chest radiography or high-resolution computed tomography and confirmed by a radiologist and pulmonologist. RPILD 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.

Anti-MDA5 was measured by a commercially available ELISA kit (MBL) in the patients with CADM and those with classic DM using serum stored from the first University of Pittsburgh outpatient (Myositis Center) or inpatient visit. The ELISA kit used a recombinant protein encompassing the entire amino acid sequence of MDA5, which was expressed and purified using a baculovirus expression system, as previously reported[12].

Myositis and other extramuscular disease activity seen in myositis patients was prospectively assessed using the Myositis Disease Activity Assessment Tool (MDAAT), a reliable and validated outcome measure previously used in multiple myositis clinical trials[19,20,21,22,23]. Using the MDAAT, we recorded physician's global disease activity, along with pulmonary, cutaneous, and muscle disease activity using a 100-mm visual analog scale (VAS). We compared the latter activity measures between different groups and correlated them with the anti-MDA5 serum levels by ELISA.

Statistical methods. Chi-squared test (Fisher's exact test when applicable) and Student t test were used to assess the association of clinical features in anti-MDA5–positive and negative patients as well as CADM and classic DM cohorts. Kaplan-Meier with log rank test was used for survival analyses (time to death in all patients) between the various groups. Cox proportional hazard model was used to compare survival outcomes after control for confounding factors (sex, ethnicity, smoking, diagnosis, age at diagnosis, and ILD). Spearman's correlation was used for correlating MDAAT disease activity by VAS with anti-MDA5 serum levels by ELISA.

RESULTS

We identified 61 patients with CADM and 61 matching classic DM controls. There were 7 patients with JDM included in the CADM cohort and 5 in the DM controls. There were 64% and 62% women, 92% and 87% whites, with a mean (SD) age of 48.2 years (16.9) and 44.8 years (17.6) in the classic DM and CADM cohorts, respectively. The frequency of anti-MDA5 positivity was similar in both the CADM (8/61, 13.1%) and classic DM (8/61, 13.1%) groups (p = 1). Other myositis autoantibodies in the patients with DM included 4 anti-Jo1, 2 anti-threonyl-tRNA synthetase (anti-PL-7), 1 anti-PL-12, 2 anti-KS, 5 small ubiquitin-like modifier activating enzyme (anti-SAE), 9 anti-Mi-2, 4 antinuclear matrix protein 2 (anti-NXP-2), 10 antitranscriptional intermediary factor 1-γ (TIF1-γ), and 4 antipolymyositis-systemic sclerosis (anti-PM-Scl). The patients with CADM included 5 anti-Jo1, 1 anti-PL-7, 3 anti-PL-12, 2 anti-KS, 2 anti-SAE, 5 anti-Mi-2, 1 anti-NXP-2, 14 anti-TIF1-γ, and 1 anti-PM-Scl. There were 56% of patients (9/16) in the anti-MDA5+ group and 76% of patients (81/106) in the anti-MDA5– group who were also antinuclear antibody–positive. One MDA5+ (CADM) and 10 MDA5– (4 DM/6 CADM) patients also had anti-SSA autoantibodies.

Clinical characteristics of anti-MDA5+ patients. Anti-MDA5+ patients (n = 16; 2 with JDM) had a mean age (SD) at diagnosis of 43 years (18.5), and 9 (56%) were women, 14 (87.5%) white, and 2 (12.5%) African American. Eight (50%) had ILD and 7 of the 8 developed RPILD; anti-MDA5 positivity was significantly associated with ILD (p = 0.04) because only 25.5% (27 of 106) of the anti-MDA5– patients had ILD. Similarly, anti-MDA5 was significantly associated with RPILD because 43.8% (7 of 16) of anti-MDA5+ patients had RPILD compared to only 0.09% (1 of 106) of anti-MDA5– patients (p < 0.0001). In 2 of the 7 with MDA5+

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RPILD, the respiratory status stabilized and they survived (1-yr and 2-yr followup in each patient). Although the most common presentation was RPILD or dyspnea in MDA5+ patients, severe cutaneous features were seen, including Gottron changes, heliotrope rash, nailfold capillary abnormalities, and puffy fingers. Severe ischemic digital and cutaneous ulcerations were also commonly observed (Table 1, Figure 1a, and Figure 1b) as well as dysphagia and myalgia. Severe ischemic digital and cutaneous ulcerations and puffy fingers were significantly associated with anti-MDA5 positivity (Table 1). Although palmar papules (Figure 1c) were observed in 4 MDA5+ patients, this feature was not systematically and prospectively evaluated on all patients in our cohort (given its more recent relevance) so we did not specifically analyze this in the MDA5+ versus MDA5– groups. Although 50% of MDA5+ patients had muscle involvement (i.e., DM), half of them had mild features and normal muscle enzymes at presentation. Detailed clinical features of all 16 anti-MDA5+ patients are described in Table 2.

Clinical associations of serum levels (ELISA) of anti-MDA5. The mean (SD) serum level of anti-MDA5 by ELISA was 206 IU/ml (48.05) in the MDA5+ patients compared to 2.64 (3.36) IU/ml in the MDA5– patients. Fifteen of 16 MDA5+ patients had serum levels > 100 IU/ml (1 with 52 IU/ml), as compared to 113/116 MDA5– patients having levels < 10 IU/ml (3 patients had levels of 28, 16, and 12 IU/ml). Further, serum levels of anti-MDA5 were significantly higher in ILD compared to no ILD [ILD: 51.0 (90.7) vs non-ILD 20.6 (59.8), p = 0.03]; however, serum levels provided no additional information on the risk of developing ILD or RPILD than the presence of the anti-MDA5 antibody. Similarly, serum levels of anti-MDA5 were significantly higher for RPILD compared to patients without RPILD [RPILD: 188.5 (81.4) vs 18.1 (55.4), p < 0.0001]. The MDAAT was prospectively scored on 50% of our patients [55% (67/122)] including 8 of the 16 MDA5+ patients and 59 of 106 MDA5– patients. Among the anti-MDA5+ patients (n = 8), serum levels of anti-MDA5 did not correlate with cutaneous, pulmonary, or physician global disease activity (p = 0.95, 0.69, 0.86, respectively).

Predictors of ILD and RPILD among anti-MDA5+ patients. Among the anti-MDA5+ patients, an older age at diagnosis was associated with ILD [mean (SD) age at diagnosis: 54 yrs (8.95) in 8 with ILD vs 32 (19.35) in 8 without ILD; p = 0.01] and RPILD [mean (SD) age at diagnosis: 53.7 yrs (9.59) in 7 with RPILD vs 34.8 (19.91) in 9 without RPILD; p = 0.03]. MDA5+ patients older than age 45 years at diagnosis had the highest risk of ILD (78%) compared to MDA5+ patients ≤ age 45 (14.3%) and MDA5– patients irrespective of their age (28.4% and 20.5% in age > 45 and ≤ 45, respectively). No other clinical features were associated with ILD or RPILD among the anti-MDA5+ patients. Among the MDA5+ patients, the serum levels of anti-MDA5 were not predictive of either ILD or RPILD development.

Clinical features of CADM. Patients with CADM were more likely to have dysphagia compared to patients with classic DM (p < 0.001; Table 1), but all other clinical features were similar in CADM versus DM (other than the muscle

Table 1. Clinical manifestations of anti-MDA5+ patients and patients with CADM compared to anti-MDA5– patients and those with classic DM at presentation. Except for p values, all data are percentages.

Clinical Features	MDA5+, n = 16	MDA5–, n = 106	p	CADM, n = 61	Classic DM, n = 61	p
ILD	50	25.5	0.04	31	26	0.46
RPILD	43.8	3.7	< 0.001	8	5	0.55
Dyspnea at presentation	56.3	27.3	0.02	32.7	24.5	0.31
Pulmonary HTN	6.2	1.8	0.34	3.3	1.6	1
Cardiomyopathy	0	0	1	0	0	1
RP	12.5	26.4	0.35	22.9	26.2	0.67
Cutaneous ulcers	37.5	3.8	< 0.001	8.2	8.2	1
Abnormal capillary microscopy	56.3	41.5	0.26	41	45.9	0.58
Digital tip ulceration	18.7	2.8	0.02	4.9	4.9	1
Heliotrope rash	50	35.9	0.28	45.9	29.5	0.06
Gottron papules/sign	68.8	41.5	0.06	39.3	49.2	0.27
Mechanic's hand	12.5	11.3	0.58	6.6	16.4	0.08
Arthralgia	18.8	13.2	0.39	9.8	18	0.19
Arthritis	12.5	12.3	0.62	8.2	16.4	0.14
Dysphagia	31.2	14.2	0.09	27.9	4.9	< 0.001
Sicca	12.5	4.7	0.22	4.9	6.5	1
Puffy fingers	25	4.7	0.01	9.8	4.9	0.49
Calcinosis	0	0	1	0	0	1
Telangiectasias	0	0.9	1	0	1.6	1
Myalgia	25	34	0.34	37.7	27.9	0.25

Anti-MDA5: Antimelanoma differentiation-associated gene 5 antibody; CADM: clinically amyopathic dermatomyositis; DM: dermatomyositis; ILD: interstitial lung disease; RPILD: rapidly progressive ILD; HTN: hypertension; RP: Raynaud phenomenon.

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Figure 1. Classic rashes of anti-MDA5–positive patients. (1a) Severe ischemic digital tip ulcerations. (1b) Severe cutaneous ulcerations. (1c) Palmar papule. anti-MDA5: antimelanoma differentiation–associated gene 5 antibody.

involvement by definition). CADM patients who were MDA5+ had more ILD (50% vs 28%; p = 0.17) and RPILD (80% vs 1%; p = 0.001) than MDA5– patients with CADM and the serum levels of anti-MDA5 were also significantly higher in those with ILD [47.6 (92.9) U/ml vs 22.7 (63.1) U/ml; p = 0.008] and RPILD [176.8 (102.5) U/ml vs 17.3 (55.12) U/ml; p < 0.001] compared to those without ILD. Among the patients with CADM, inflammatory arthralgias and mechanic's hand were associated with ILD (p = 0.004 and 0.004, respectively).

Survival outcomes. We have previously reported poor survival among patients with anti-MDA5 positivity secondary to high frequency of RPILD associated with anti-MDA5[16]. In addition, in our study we found that although serum levels of anti-MDA5 antibody level were similarly strongly associated with poor survival (p = 0.014), they provided no additional risk or predictive value for survival beyond anti-MDA5 positivity.

DISCUSSION

Patients with CADM have the classic rash(es) of DM but no objective muscle weakness. If the rash is subtle and there are no other well-recognized features of autoimmune disease, pulmonary involvement can be missed. Although we had

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Table 2. Key clinical features of the 16 anti-MDA5+ patients.

Patients	Age at Diagnosis, Yrs, Sex	Diagnosis	Rashes	Muscle Involvement	Pulmonary	Survival/prognosis	Other Key Features
1	47 M	Classic DM	Nonspecific rash on extremities	Mild proximal muscle weakness	ILD (RPILD)	Developed respiratory failure requiring intubation and died within 1 month	Myalgia, dysphagia, abnormal nailfold capillary
2	38 M	Classic DM	Heliotrope rash, Gottron papules, necrotic ulcers	Mild proximal muscle weakness	No ILD	Alive (4-yr followup)	Dysphagia
3	56 F	Classic DM	Gottron papules, cutaneous ulcers, digital tip ulceration with gangrene, heliotrope rash, palmar papules	Mild proximal muscle weakness	ILD	Alive (3-yr followup)	Sicca, RP, dysphagia, abnormal nailfold capillary, arthralgia
4	39 F	Classic DM	Heliotrope rash, Gottron papule/sign	Mild proximal muscle weakness	No ILD	Alive (11-yr followup)	Myalgia, arthritis, abnormal nailfold capillary
5	55 M	Classic DM	Mechanic's hand, heliotrope rash	Mild proximal muscle weakness	ILD (RPILD)	Developed respiratory failure requiring intubation and died within 1 yr	RP, arthralgia, abnormal nailfold capillary
6	46 M	Classic DM	Gottron papules	Moderate proximal muscle weakness	ILD (RPILD) and PAH	Respiratory status stabilized and patient remained alive (2-yr followup)	Myalgia, dysphagia, abnormal nailfold capillary
7	9 F	JDM	NA	Moderate proximal muscle weakness	No ILD	Alive (14-yr followup)	Dysphagia
8	2 F	JDM	NA	Severe proximal muscle weakness	No ILD	Alive (1-yr followup)	
9	41 F	CADM	Gottron sign, malar rash, palmar papules	No weakness	ILD (RPILD)	Developed respiratory failure requiring intubation and died within 1 month	
10	56 M	CADM	Gottron sign, violaceous rashes over extensor areas of hand, forearm, elbow, and knees, periorbital edema/rash and V-neck rash, livedoid rash	No weakness	ILD (RPILD)	Developed respiratory failure requiring intubation and died within 1 month	
11	18 M	CADM	Gottron sign, digital tip ulcerations and cutaneous ulcerations, heliotrope rash	No weakness	No ILD	Alive (2-yr followup)	Abnormal capillary microscopy
12	49 F	CADM	Gottron papules/sign, heliotrope rash	No weakness	No ILD	Alive (5-yr followup)	Abnormal nailfold capillary, mechanic's hand
13	58 F	CADM	Palmar papules and cutaneous ulcerations, Gottron papules/sign, heliotrope rash	No weakness	ILD (RPILD)	Developed respiratory failure requiring intubation and died within 1 yr	Abnormal nailfold capillary, arthralgia, arthritis, myalgia
14	44 F	CADM	Nonspecific (biopsy-proven)	No weakness	No ILD	Alive (19-yr followup)	
15	54 F	CADM	Gottron papules, severe cutaneous ulcers	No weakness	No ILD	Alive (8-yr followup)	Sicca, RP, abnormal nailfold capillary
16	70 M	CADM	Gottron papules, cutaneous ulcers, digital tip ulceration, palmar papules	No weakness	ILD (RPILD)	Respiratory status stabilized and patient remained alive (1-yr followup)	Abnormal nailfold capillary

Anti-MDA5: antimelanoma differentiation-associated gene 5 antibody; CADM: clinically amyopathic dermatomyositis; DM: dermatomyositis; JDM: juvenile DM; ILD: interstitial lung disease; RPILD: rapidly progressive ILD; NA: specific rash details not available; RP: Raynaud phenomenon; PAH: pulmonary arterial hypertension.

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noted a similar frequency of anti-MDA5 positivity in both CADM and classic DM[16], in a total of 233 MDA5+ Japanese patients, CADM was more frequent than DM (75% vs 39%; p = not significant)[13]. Thus, the association of anti-MDA5 with subsets of DM may vary among different ethnic groups.

In our experience, anti-MDA5 positivity was significantly associated with severe rashes including digital ischemia and cutaneous ulcerations, as well as both ILD and RPILD. In addition we have previously reported that anti-MDA5 positivity was significantly associated with poor survival compared to the MDA5– cohort primarily owing to the high frequency of patients presenting with RPILD[16]. Although the pulmonary features are similar to the Asian reports, the latter studies do not consistently report the cutaneous features frequently seen in our cohort and other US centers[14]. For example, one Japanese study noted ILD and RPLID in MDA5+ patients, but other clinical DM features of cutaneous ulcers were not specifically seen[7]. Another cross-sectional Japanese report of patients with DM possessing either anti-MDA5, –Mi-2, or TIF1-γ noted that the MDA5+ patients had the highest frequency of ILD and skin ulcers among the 3 groups[9]. The presence of skin ulcers was not of prognostic significance in these patients. More recently, in a single-center cohort of 64 consecutive Chinese patients with PM/DM, it was more common to find ILD and RPLID in the anti-MDA5+ group, but other clinical features were similar, including cutaneous ulcerations[11].

Our observations have both similarities and differences with reports from other US centers. In a cohort of 77 patients with DM from a Stanford dermatology clinic, anti-MDA5 was associated with ILD and a unique cutaneous phenotype consisting of tender palmar papules and/or skin ulceration[20], but the investigators did not assess RPLID. Another myositis center showed that anti-MDA5+ patients were more likely to have features similar to the antisynthetase syndrome, but RPILD was again not found[15]. Conversely, in our patients with CADM and classic DM, the antisynthetase syndrome features of arthritis and mechanic's hands were similar in both MDA5+ and MDA5– patients. We noted a phenotype of digital tip ulcerations, puffy fingers, and cutaneous ulcers, and although palmar papules were not systematically recorded in our database, we certainly observed this feature in many of our MDA5+ patients. Circulatory compromise and microvascular injury is a hallmark of many systemic autoimmune diseases and the rationale behind the apparent vascular targeting seen with this autoantibody is unclear but worthy of additional study.

We also found that age was an important risk factor among MDA5+ patients for developing ILD (p = 0.01) or RPILD (p = 0.03), perhaps guiding physicians to regard older patients as being at higher risk for ILD at diagnosis or followup. Although we had the opportunity to quantify serum levels of anti-MDA5 by ELISA, this provided no additional predictive value for survival beyond the dichotomous presence or absence of MDA5. Moreover, anti-MDA5 levels were not associated with physician-reported global, pulmonary, or cutaneous disease activity, similar to the finding that anti-MDA5 titers failed to track with clinical course in another MDA5+ myositis cohort in the United States[15].

In this retrospective cohort study from a single academic center, there were the usual limitations of selection bias, small sample size, generalizability of the findings, and missing data. However, our data are prospectively collected as patients are seen and their clinical data are then entered into our computer database. Further, we attempted to minimize selection bias by constructing the CADM and classic DM groups without knowledge of the survival or pulmonary outcomes. Another study limitation relates to more MDAAT data being available on patients who survived as compared to those who died, excluding patients with more severe conditions from the analysis of disease activity, potentially biasing the disease activity correlation results.

Anti-MDA5 is associated with a unique clinical phenotype consisting of ILD, RPILD, digital tip ulcerations, puffy fingers, and cutaneous ulcers in US patients with myositis. Classifying patients with DM according to their autoantibody status and clinical features may guide clinicians to focus on particular high-risk complications during the followup of individual patients.

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