Systematic retrospective study of 64 patients with anti-Mi2 dermatomyositis: A classic skin rash with a necrotizing myositis and high risk of malignancy

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Letter

Research letter

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To the Editor: Dermatomyositis (DM) is an autoimmune myopathy associated with the presence of a specific skin rash and characteristic morphologic features, including perifascicular pathology without myofiber necrosis. However, the clinical and morphologic spectrum of DM remains heterogeneous. It is now recognized that DM-specific autoantibodies are useful in defining more homogeneous subsets of patients with DM.[1] The anti-Mi2 antibody was discovered more than 40 years ago; nonetheless, few studies have described its phenotype, and these have included only a limited number of patients.[2] In this study, we aim to characterize the anti-Mi2 DM phenotype with a focus on the cutaneous and muscular features, including a myopathologic description of the skeletal muscle biopsies, and evaluate its association with cancer.

This was an observational, multicenter study (16 medical centers) from July 2013 through January 2017. Anti-Mi2$^+$ and anti-Mi2$^-$ (control) patients with DM were included if they presented with (1) DM skin rash as defined by the European NeuroMuscular Center[3] and/or Sontheimer[4] criteria and (2) DM-specific antibodies (anti-Mi2, anti-NXP2, anti-MDA5, anti-TIF1γ, or anti-SAE) and/or myopathologic features of DM (for seronegative patients) according to the European NeuroMuscular Center criteria.[3] All muscle biopsy samples from the Pitié-Salpêtrière Hospital (anti-Mi2$^+$ patients with DM, n = 20; control patients, n = 32) were reviewed.

Sixty-four anti-Mi2$^+$ patients with DM were included. The median age at diagnosis was 55.5 years (first and fourth quartile, 38.1-65.8), and patients were mainly females (60.9%; n = 39/64). Comparison of features of anti-Mi2$^+$ patients with DM and those of control patients (n = 55) is shown in Table I. Anti-Mi2$^+$ patients with DM presented more frequently with a classic DM skin rash (including Gottron papules/sign and/or heliotrope rash and/or periungual erythema and/or violaceous rash including Holster sign) without additional skin changes such as calcinosis, ulcers, panniculitis, and/or mechanic hands (82.8% vs 45.3%; $P = .0004$) (Table I).

All anti-Mi2$^+$ patients with DM except 1 (amyopathic) had proximal muscle weakness (Table I), and in more than half of these patients, muscle weakness was severe (Medical Research Council 5 scale, ≤3). Consistent with the presence of high creatine kinase levels (Table I), anti-Mi2$^+$ patients with DM had increased myofiber necrosis (90% vs 26% in control patients; $P < .0001$) encountered in both the perifascicular and centrofascicular areas. A perifascicular atrophy was observed in all anti-Mi2$^+$ patients with DM.

Compared with the age- and sex-matched expected cancer rate in the general French population, the anti-Mi2$^+$ patients with DM had an increased risk of cancer, with a standardized incidence ratio of 5.1 (95% confidence interval [CI]: 3.0-8.6) ($P < .001$). The median time between DM diagnosis and malignancy diagnosis was 61.5 days [95% CI: -105.8 to 237.5]. All but 1 of the anti-Mi2$^+$ patients with DM who had cancer-associated myositis were older than 50 years. Patients with malignancy had a worse prognosis with higher mortality rate compared with patients without cancer ($P = .008$) (Fig 1).

Although patients with DM with anti−TIF1-γ, anti-MDA5, anti-SAE, and anti-NXP2 may display distinct cutaneous features in addition to the classic DM skin rash,[5] we observed that anti-Mi2$^+$ patients with DM present a classic DM skin rash more frequently. For the first time, to our knowledge, we showed that anti-Mi2$^+$ patients with DM present extracutaneous characteristics, including a necrotizing myositis and an increased risk of malignancy. These findings strengthen the importance of DM-specific antibodies to delineate more homogeneous DM phenotypes.

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Table I. Comparison of cutaneous, muscular, extracutaneous, and extramuscular manifestations of anti-Mi2$^+$ and anti-Mi2$^-$ patients

Features	Anti-Mi2$^+$ DM, n (%) n = 64	Anti-Mi2$^-$ DM, n (%) n = 55	Fisher's test, n (%) *P* value
Cutaneous features			
Alopecia	1/42 (2.4)	7/55 (12.7)	.13
Calcinosis cutis	1/56 (1.8)	6/55 (10.9)	.06
Panniculitis	2/42 (4.7)	3/55 (5.5)	>.99
Cutaneous ulceration	2/56 (3.6)	10/55 (18.2)	.02
Mechanic hands	6/56 (10.7)	7/55 (12.7)	.78
Heliotrope rash	41/64 (64.1)	34/55 (61.8)	.8
Gottron papules/sign	38/53 (71.7)	21/55 (38.2)	.0005
Periungual erythema	36/56 (64.3)	25/55 (45.5)	.05
Holster sign	12/55 (21.8)	2/55 (3.6)	.008
Muscular features			
Myalgia	15/23 (65.2)	48/54 (89)	.02
Proximal weakness	61/64 (95.3)	49/55 (89.1)	.35
Severe weakness (MRC score, ≤3)	29/54 (53.7)	35/55 (66)	.02
Elevated CK level	58/64 (90.6)	46/55 (83.6)	.28
CK level (IU/L)*	3748 (1159-8799)	1680 (893-5818)	.23
Myopathic EMG	32/37 (86.5)	34/42 (81)	.56
Abnormal muscle MRI†	20/33 (62.5)	30/53 (56.6)	.87
T2 hypersignal	15/17 (88.2)	23/31 (74.2)	.46
T1 fat replacement	6/17 (35.3)	9/25 (36)	>.99
Extracutaneous and extramuscular features			
Raynaud phenomenon	8/63 (12.7)	12/54 (22.2)	.26
Arthritis/arthralgia	17/63 (27)	23/55 (41.8)	.13
Dyspnea	1/10 (10)	31/52 (59.6)	.01
ILD	13/34 (38.2)	10/52 (19.2)	.08
FEV < 70%	2/11 (18.2)	9/47 (19.2)	>.99
FCV < 70%	1/24 (4.2)	7/46 (15.2)	.25
DLCOc < 70%	3/22 (13.6)	14/23 (60.9)	.002
Myositis specific antibodies	64/64 (100)	20/55 (36.4)	<.0001
Anti-Mi2	64/64 (100)	0/55 (0)	<.0001
Anti-MDA5	—	9/37 (24.32)	—
Anti-NXP2	—	3/31 (9.68)	—
Anti-SAE1/2	—	3/31 (9.68)	—
Anti-TIF1γ	—	5/32 (13.51)	—

DLCOc, Corrected carbon monoxide diffusion capacity; *CK*, creatine kinase; *DM*, dermatomyositis; *EMG*, electromyogram; *FCV*, forced vital capacity; *FEV*, forced expiratory volume; *ILD*, interstitial lung disease (defined on chest computed tomography scan); *MRC*, Medical Research Council; *MRI*, magnetic resonance imaging.

*The CK level values are presented as mean (range).

†Muscle MRI abnormalities are defined as sequence T1 inversion-recuperation or fat-saturated gadolinium-enhanced T2-weighted or gadolinium-enhanced T1-weighted hypersignals.

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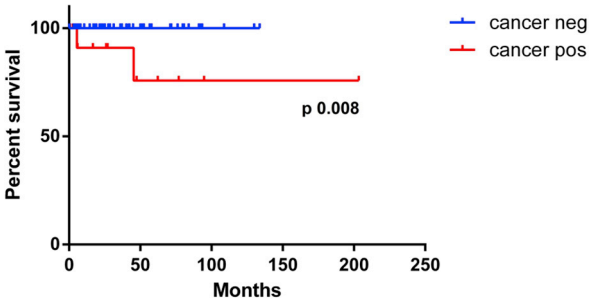

Fig 1. Survival curve in anti-Mi2$^+$ patients with dermatomyositis with or without malignancy. *neg*, Negative; *pos*, positive.

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REFERENCES

1. Benveniste O, Stenzel W, Allenbach Y. Advances in serological diagnostics of inflammatory myopathies. *Curr Opin Neurol*. 2016;29(5):662-673.
2. Hamaguchi Y, Kuwana M, Hoshino K, et al. Clinical correlations with dermatomyositis-specific autoantibodies in adult Japanese patients with dermatomyositis: a multicenter cross-sectional study. *Arch Dermatol*. 2011;147(4):391-398.
3. Mammen AL, Allenbach Y, Stenzel W, Benveniste O; ENMC 239th Workshop Study Group. 239th ENMC International Workshop: classification of dermatomyositis, Amsterdam, The Netherlands, 14-16 December 2018. *Neuromuscul Disord*. 2020;30:70-92.
4. Sontheimer RD. Dermatomyositis: an overview of recent progress with emphasis on dermatological aspects. *Dermatol Clin*. 2002;20(3):387-408.
5. Wolstencroft PW, Fiorentino DF. Dermatomyositis clinical and pathological phenotypes associated with myositis-specific autoantibodies. *Curr Rheumatol Rep*. 2018;20(5):28.

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