Clinical, histologic and prognostic features of clinically amyopathic dermatomyositis

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Abstract

Objective

To characterise clinical amyopathic dermatomyositis (CADM) from a clinical, histological, and prognostic perspective.

Methods

We retrospectively recorded data from our DM cohort. Patients were categorised into three groups: classic DM, hypomyopathic DM (HDM), characterised by normal muscle strength and evidence of muscle involvement in laboratory tests and/or instrumental examinations and CADM, featured by normal muscle strength and unremarkable findings in both laboratory tests and instrumental examinations. Available muscle biopsies from each group were also compared.

Results

Our cohort included 63 DM (69.2%), 12 HDM (13.2%) and 16 CADM (17.6%) patients. Compared to DM, CADM patients were younger at onset and diagnosis (45.5±17 vs. 57±18, and 46±17 vs. 58±18 years, respectively; $p<0.05$). They were more likely to test positive for anti-MDA5 (37.5% vs. 4.8%) and anti- TIF1-γ (31.3% vs. 6.3%), had a higher incidence of arthritis (37.5% vs. 12.6%) and interstitial lung disease (ILD) (43.8% vs. 15.9%) (all comparisons with $p<0.05$). Muscle biopsies were available for 44 DM, 7 CADM, and 11 HDM patients, revealing similar sarcolemma MHC-I expression rates. Five-year survival rates were comparable across groups (DM: 74.6%, CADM: 75%, HDM: 83.3%). Cox analysis indicated the main mortality predictors in overall cohort were ILD (HR: 3.57, CI: 1.11-11.5) and cancer (HR: 3.67, CI: 1.17-11.5), not CADM (HR: 1.46, CI: 0.33-6.68).

Conclusion

CADM patients differ in disease onset, autoantibody profiles, joint and lung involvement. While laboratory and instrumental tests have not shown muscle involvement in CADM, many muscle biopsies have shown MHC-I overexpression.

Key words

dermatomyositis, prognosis, connective tissue disease

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Introduction

Dermatomyositis (DM) is a rare autoimmune disease that falls under the spectrum of idiopathic inflammatory myopathies (IIMs) (1, 2). The hallmark characteristics of DM include skin involvement, characterised by typical lesions, together with muscle weakness, especially in the proximal body muscles (1-3). A subset of DM patients maintains normal muscle strength and is termed clinical amyopathic dermatomyositis (CADM) (4). Some patients, however, have laboratory or instrumental signs of muscle involvement and are classified as hypomyopathic dermatomyositis (HDM) (1).

In the real-world setting, CADM patients do not undergo a muscle biopsy, making the diagnosis of pure amyopathic DM (ADM) challenging. In fact, the lack of muscle involvement often means there is no compelling reason to perform a biopsy. The older classification criteria by Bohan and Peter (5) were unable to identify all cases of DM, as they gave high importance to muscle manifestations. This led to the development of new criteria (6, 7). The term "ADM" was initially coined by Euwer and Sontheimer in 1993 (8), who were the first to propose the inclusion of ADM as a subcategory of IIMs. ADM is defined by the presence of hallmark cutaneous findings of DM, with an absence of any clinical or laboratory evidence of muscle disease for 6 months or longer (9).

The most recent ACR/EULAR 2017 criteria were studied with the aim of classifying patients with IIM, including ADM. After classifying patients as having IIM, they can then be sub-classified using the classification tree. According to this system, patients classified as ADM exhibit typical skin lesions without the presence of objective symmetric muscle weakness. Notably, muscle biopsy is not required to classify patients with ADM (7).

Using data from our cohort of DM patients enrolled in the INflammatory MYositis REgistry (INMYRE), our objective was to characterise clinical amyopathic dermatomyositis (CADM) from a clinical, histological, and prognostic perspective.

Materials and methods

Population

We conducted a monocentric retrospective observational study, which included DM patients from the Rheumatology Unit of Policlinico of Bari, spanning from 2010 to 2022. We retrospectively analysed the medical charts of DM patients registered in INMYRE (study no. 6229, approval no. 84762,2020/11/06; comitatoetico@policlinico.ba.it).

All patients included in this study were classified as DM according to the 2017 ACR/EULAR classification criteria[7] and were categorised into three groups. Classic DM patients encompassed those who displayed muscle weakness at clinical examinations, as detected by the manual muscle test (MMT8) score. HDM patients included those who had normal muscle strength (*i.e.* MMT8 150/150) after diagnosis and throughout a minimum 6-month follow-up period (9), yet showed slightly elevated muscle enzyme levels or abnormal findings on electromyography (EMG) or thigh magnetic resonance imaging (MRI). Of note, patients with creatine kinase (CK) levels above 1000 UI/L were classified as having DM, even though they did not exhibit a muscle strength deficit. On the other hand, patients were categorised as having CADM if muscle strength and muscle enzyme levels were normal; and EMG and/or MRI findings were unremarkable for at least 6 months after diagnosis (1, 9). Clinical and demographics data analysed in the present study were retrospectively obtained by individual electronic medical records reviewed by rheumatologists with recognized expertise in the diagnosis and management of IIM. Disease onset was considered from the observation of the first muscle (weakness), lung, joint or skin symptom/sign related to DM. The following data were recorded: demographics such as age at disease onset and diagnosis, gender, therapy, outcome at last follow-up visit (alive/death) and cause of death; other clinical manifestations such as Raynaud phenomenon, arthritis and dysphagia (the latter was confirmed with fibre-optic endoscopic evaluation of swallowing) were also obtained (10). Interstitial lung disease (ILD) was de-

fined by high-resolution CT scan of the chest. Rapidly progressive-ILD (RP-ILD) was defined as a critical condition characterised by severe hypoxaemia (PaO2/FiO2 ratio 200) that worsened within 3 months from the onset of ILD upon exclusion of other possible causes (pulmonary infections, heart failure, embolism) (11). Main clinical manifestations were recorded at diagnosis and at the last clinical assessment. Cancer-associated myopathy (CAM) was defined as neoplasia detection before or after 3 years DM onset (12).

Laboratory assessment

Maximum levels of CK were recorded during follow-up and compared with the reference ranges of laboratory centers to assess the altered values of muscle enzymes. Myositis-specific antibodies (MSA) (Jo1, PL7, PL12, EJ, OJ, Mi2 a/b, TIF1-γ, MDA5, NXP2, SAE1/2, SRP) and myositis-associated antibodies (Ku, PM-Scl 100/75, Ro-52) were searched by the same line blot assay, performed according to the manufacturer's recommendations (Euroline Autoimmune Inflammatory Myopathies, Euroimmun, Germany). Patients with autoantibodies against Aminoacyl tRNA Synthetase (ARS) (*e.g.* Jo1, PL-7, PL-12, OJ or EJ) or against PM/Scl proteins or who fulfilled criteria for other connective tissue diseases were excluded from the analysis because it is considered as a distinct disease (13).

Histological and immunohistochemical analysis

Muscle samples were obtained with open surgery by a dedicated surgeon (D.D.) and soon after fresh-frozen in isopentane pre-cooled in liquid nitrogen. All frozen samples were analysed in the Department of Neurophysiopathology (University of Bari), following standardised procedures and according to a routine protocol. All patients had given informed consent for muscle biopsy as part of the diagnostic workout and for their medical records to be used for research purposes. As a clinical practice in our Rheumatologic Unit, we suggest a muscle biopsy for all patients affected by DM, selecting the muscle based on the outcome of the manual muscle strength test, EMG and thigh MRI examinations. In the case of CADM, the biopsy is carried out on a proximal muscle (deltoid or quadriceps). Cryostat sections (7 μm thick) of muscle biopsy specimens were used. The following stains were studied for morphological characterisation: haematoxylin/eosin (H&E) and modified Gömöri trichrome (MGT). Immunohistochemical analysis was performed using the following antibodies: mouse anti-major histocompatibility complex type I (MHC-I) (1:50; Dako, Carpinteria, USA: M0736), anti-CD4 (1:40; Dako: M7310), anti-CD8 (1:40; Dako: M7103), anti-CD68 (1:50; Dako: M0876), anti- CD20 (1:100; Dako: M0755), anti-CD56 (1:50; Dako: M7304), anti-C5b-9 complex (1:25; Dako: M0777) and anti CD31 (1:30; Dako: M0823). Perifascicular atrophy was defined as the presence of myofibres with a lesser diameter under 40μm for male and under 30μm for female affecting >6 fibres along one edge of

Table I. Comparisons between dermatomyositis, clinical amyopathic dermatomyositis and hypomyopathic dermatomyositis.

Variables	DM (63 pts.)	HDM (12 pts.)	CADM (16 pts.)
Female, n.(%)	54 (85.7)	7 (58.3)	12 (75)
Age at onset, mean (SD)	57 (18)	47 (13)	45.5 (17)*
Age at diagnosis, mean (SD)	58 (18)	48 (13)	46 (17)*
diagnostic delay (months), median (IQR)	8 (4-9)	9.5 (4-15)	9 (3-14)
Follow-up duration (months), median (IQR)	41 (12-86)	56 (16-70)	38 (11-50)
ANA ≥ 1/160	55 (87.3)	9 (75)	13 (81.3)
Myositis-specific autoantibodies, n.(%)			
Mi2	17 (27)	0 (0)	0 (0)
MDA5	3 (4.8)	2 (16.7)	6 (37.5)*
TIF1-γ	4 (6.3)	0 (0)	5 (31.3)*
NXP2	5 (7.9)	0 (0)	0 (0)
SAE1/2	7 (11.1)	1 (8.3)	1 (6.3)
Negative	27 (39.7)	9 (75)	4 (25)#
Ro52, n.(%)	9 (14.3)	2 (16.7)	4 (25)
CK maximum (U/L)[+], median (IQR)	971 (320-2457)	297 (124-728)	117 (85-197)*#
Skin involvement at onset, n.(%)	57 (90.5)	10 (83.3)	15 (93.8)
Heliotrope rash, n.(%)	59 (93.7)	10 (83.3)	15 (93.8)
Gottron's papules/sign, n.(%)	58 (92.1)	11 (91.7)	15 (93.8)
Shawl-sign/V-sign, n.(%)	45 (71.4)	7 (58.3)	11 (68.8)
Calcinosis, n.(%)	5 (7.9)	2 (16.7)	1 (6.3)
Arthritis at onset, n.(%)	5 (7.9)	1 (8.3)	4 (25)
Arthritis at follow-up, n.(%)	8 (12.6)	3 (25)	6 (37.5)*
ILD at onset, n.(%)	4 (6.3)	2 (16.7)	4 (25)
ILD at follow-up, n.(%)	10 (15.9)	3 (25)	7 (43.8)*
RP-ILD, n.(%)	3 (4.8)	1 (8.3)	2 (12.5)
Cancer, n.(%)	10 (15.9)	3 (25)	3 (18.8)
Raynaud, n.(%)	10 (16.4)	3 (21.4)	4 (25)
Dysphagia, n.(%)	31 (49.2)	5 (41.6)	4 (25)
Azathioprine, n.(%)	32 (52.8)	7 (58.3)	8 (50)
Methotrexate, n.(%)	43 (68.3)	8 (66.7)	8 (50)
Mycophenolate Mofetil, n.(%)	11 (17.5)	4 (33.3)	4 (25)
Cyclophosphamide, n.(%)	2 (3.2)	2 (16.7)	3 (18.8)
Hydroxychloroquine, n.(%)	12 (19)	1 (8.3)	4 (25)
Cyclosporine, n.(%)	3 (4.8)	2 (16.7)	4 (25)
Rituximab, n.(%)	8 (12.7)	1 (8.3)	5 (31.3)
Intravenous Immunoglobulin, n.(%)	9 (14.3)	2 (16.7)	1 (6.3)
Glucocorticoid (any dose), n.(%)	63 (100)	12 (100)	16 (100)
Thigh MRI assessment, n.(%)	44 (69.8)	8 (66.7)	10 (62.5)
EMG assessment, n.(%)	40 (63.5)	9 (75)	11 (68.6)
Muscle biopsy, n.(%)	44 (69.8)	11 (91.6)	7 (43.7)#*

ANA: antinuclear antibodies; CADM: clinical amyopathic DM; CK: creatine kinase; DM: dermatomyositis; EMG: electromyography; HDM: hypomyopathic DM; ILD: interstitial lung disease; IQR: interquartile range; MRI: Magnetic Resonance Imaging; RP-ILD: rapidly progressive ILD; SD: standard deviation.

[+]Maximum level of CK according to laboratory centres: 250 U/L for men and 200 U/L for women.

*$p<0.05$ *vs*. DM; #$p<0.05$ *vs*. HMD.

the fasciculus (14). Presence or absence of each antigen, perifascicular atrophy and myofibre degeneration/necrosis were assessed in all biopsies.

Statistics

The Kolgomorov-Smirnov test was used to evaluate the distribution of continuous variables. Demographics and disease characteristics were evaluated using standard descriptive statistics. Categorical variables were expressed as number or percentage; continuous variables as mean (S.D.) or median and interquartile rage (IQR). Comparisons between groups were performed by Fisher's exact test and Student's t test followed by post-hoc tests with Bonferroni correction, when appropriate. A p-value <0.05 was considered statistically significant. Survival from disease onset was estimated using Kaplan-Meier (K-M) life-table method and differences between groups were compared using the log-rank test. Univariate and multivariate Cox regression models were built to identify risk factors for death. The multivariate model included only those variables that were significantly positive in the univariate analysis. Statistical analysis was conducted using IBM SPSS Software (v. 21.0, Armonk, NY, USA).

Results

Clinical features

The study cohort comprised 63 patients with classic DM (69.2%), 12 with HMD (13.2%) and 16 (17.6%) with CADM. All data are reported in Table I. Compared to those with classic DM, CADM patients had younger age at disease onset (mean 45.5±17 years *vs*. 57±18 years, p<0.05) and disease diagnosis (mean 46±17 years *vs*. 58±18 years, p<0.05) compared to classic DM. A higher percentage of patients with CADM showed autoantibodies against MDA5 (37.5% *vs*. 4.8%, p<0.05) and TIF1-γ (31.3% *vs*. 6.3%, p<0.05) compared to classic DM patients. On the other hand, a larger percentage of HDM patients presented with seronegative disease when compared to CADM (75% *vs*. 25%, p<0.05). Based on clinical characteristics, CADM patients were more susceptible to arthritis (37.5% *vs*. 12.6%, p<0.05) and ILD (43.8% *vs*. 15.9%, p<0.05) than those with classic DM. No significant differences were noted in the presence of RP-ILD subset and CAM across all three groups. As expected, the highest CK values were observed in classic DM [median (IQR) 971 (320-2457) UI/L], followed by HDM [median (IQR) 297 (124-728) UI/L] and CADM [median (IQR) 117 (85-197) UI/L] (all p<0.01). No significant differences were found between the characteristics of classic DM and HDM.

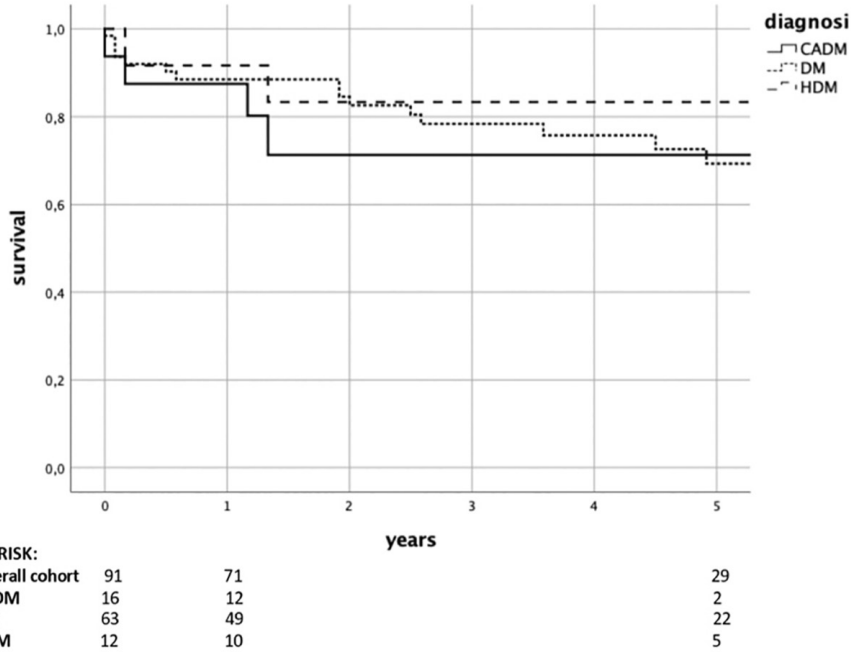

Fig. 1. Kaplan-Meier analysis of 5-years survival since DM presentation, comparison between classic dermatomyositis (DM), hypomyopathic dermatomyositis (HDM) and clinically amyopathic dermatomyositis (CADM).

Table II. Univariate and multivariate cox regression model assessing survival in overall dermatomyositis cohort.

	Univariate			Multivariate		
Variables	HR	95% CI	p-value	HR	95% CI	p-value
Female	0.60	0.23-1.55	0.293			
Age at diagnosis	**1.05**	**1.02-1.08**	**0.002**	1.02	0.92-1.11	0.669
Age at onset	**1.05**	**1.02-1.08**	**0.001**	0.99	0.89-1.13	0.947
diagnostic delay	0.89	0.78-1.01	0.062			
Mi2 *vs*. other	0.67	0.20-2.28	0.523			
TIF1g *vs*. other	**4.1**	**1.49-11.3**	**0.006**	2.48	0.60-10.1	0.211
SAE1/2 *vs*. other	1.74	0.51-5.94	0.372			
MDA5 *vs*. other	2.09	0.70-6.24	0.185			
Seronegative for MSA *vs*. other	0.43	0.17-1.12	0.084			
Ro52	**3.73**	**1.48-9.34**	**0.005**	2.12	0.62-7.22	0.228
Arthritis	0.16	0.02-1.21	0.076			
ILD	**3.72**	**1.56-8.88**	**0.003**	**3.57**	**1.11-11.5**	**0.033**
CK maximum	1	1-1	0.432			
Cancer	**3.65**	**1.5-8.9**	**0.004**	**3.67**	**1.17-11.5**	**0.026**
CADM *vs*. DM+HDM	1.46	0.33-6.58	0.617			

CADM: clinical amyopathic DM; CI: confidence interval; CK: creatine kinase; DM: dermatomyositis; HDM: hypomyopathic DM; HR: hazard ratio; ILD: interstitial lung disease.

Prognosis

The median interquartile range (IQR) of follow-up duration for our cohort was 41 (14-71) months. During this period, 22 patients died: 16 with classic DM (4 from cancer, 4 from ischaemic heart disease, 4 from ILD progression and 4

Table III. Histologic characteristics of dermatomyositis, clinical amyopathic dermatomyositis and hypomyopathic dermatomyositis.

Variables	DM (44 pts.)	HDM (11 pts.)	CADM (7 pts.)
Female, n.(%)	37 (84.1)	7 (63.6)	6 (85.7)
Age at biopsy, mean (SD)	56 (19)	48 (13)	46 (15)
Myositis-specific autoantibodies, n.(%)			
Mi2	13 (29.5)	0 (0)	0 (0)
MDA5	1 (2.3)	1 (9.1)	3 42.9)*
TIF1-γ	4 (9.1)	0 (0)	2 (28.6)
NXP2	5 (11.4)	0 (0)	0 (0)
SAE1/2	4 (9.1)	1 (9.1)	1 14.3)
Negative	17 (38.7)	9 (81.8)	1 (14.3)#
CK maximum (U/L), mean (SD)	1220 (278-3016)	367 (124-791)	124 (103-188)*#
Myofibre in degeneration/necrosis, n.(%)	25 (56.8)	4 (36.4)	2 (28.6)
Regenerating fibres, n.(%)	26 (59.1)	4 (36.4)	2 (28.6)
MAC on fibres, n.(%)	21 (47.7)	3 (27.3)	1 (14.3)
MAC on capillaries, n.(%)	23 (52.3)	3 (27.3)	4 (57.1)
MHC-I expression, n.(%)	28 (63.6)	7 (63.6)	5 (71.4)
CD4 infiltrates, n.(%)	5 (11.4)	0 (0)	1 (14.3)
CD8 infiltrates, n.(%)	6 (13.6)	2 (18.2)	0 (0)
CD20 infiltrates, n.(%)	7 (15.9)	0 (0)	1 (14.3)
CD68 infiltrates, n.(%)	26 (59.1)	4 (36.4)	3 (42.9)
Perifascicular atrophy, n.(%)	25 (56.8)	8 (72.2)	2 (28.6)
Normal muscle tissue, n. (%)	2 (4.5)	1 (9.1)	2 (28.6)

CADM: clinical amyopathic DM; CK: creatine kinase; DM: dermatomyositis; HDM: hypomyopathic DM; MAC: membrane attack complex; MHC-I: major histocompatibility complex type I.
*p<0.05 *vs*. DM; #p<0.05 *vs*. HMD.

from unknown causes), 2 with HDM (1 from cancer and 1 from ILD progression), and 4 with CADM (1 from cancer, 2 from ILD progression and 1 from an infection). The 1- and 5-year survival rates (Fig. 1) were comparable among the three groups: 90.4% for classic DM, 91.7% for HDM and 87.5% for CADM at 1 year (log-rank: 0.29, p=0.86); 74.6% for classic DM, 83.3% for HDM and 75% for CADM at 5 years (log-rank: 0.32, p=0.85). A multivariate Cox regression model (Table II), adjusted for variables associated with death in the univariate model, showed that the independent predictors of death were ILD (HR: 3.57, 95% CI 1.11–11.5) and cancer (HR: 3.67, 95% CI 1.17–11.5).

Histology

Sixty-two muscle biopsies were available for analysis: 44 from DM patients (13 anti-Mi2+, 1 anti-MDA5+, 5 anti-NXP2+, 4 anti-SAE1/2+, 4 anti-TIF1-γ+, 17 seronegative) 7 from CADM patients (3 anti-MDA5+, 2 anti-TIF1-γ, 1 anti-SAE1/2, 1 seronegative), and 11 from HDM patients (1 anti-MDA5+, 1 anti-SAE1/2+, 9 seronegative) (Table III and Fig. 2). Patients with CADM displayed a lower percentage of muscle tissue exhibiting myofibre degeneration/necrosis and perifascicular atrophy compared to DM and HDM patients; however, these differences were not statistically significant. Notably, a similar increase in sarcolemma MHC-I expression was observed across DM, CADM, and HDM patients, with prevalence rates of 63.6% (28/44 patients), 71.4% (5/7 patients), and 63.6% (7/11 patients), respectively. Among CADM patients, only two out of seven showed no histological signs of myopathy on muscle biopsy. Both these two patients had CAM: one exhibited a gastrointestinal stromal tumour (MDA5 positive CADM) and the other a melanoma skin cancer (seronegative CADM).

Discussion

CADM represents a variant of DM characterised by the lack of muscle weakness related to the pathology (4). Consequently, muscle biopsies are often not performed. In our study, we assessed differences from clinical, prognostic, and histopathological perspectives in an Italian monocentric cohort of patients with DM, HDM and CADM.

Epidemiologically, we found that patients with CADM presented with a younger age at the onset of the disease and at diagnosis. This finding appears to be confirmed by other Asian cohorts (15, 16), where the mean age at diagnosis is under 50 years, suggesting that the onset of CADM forms may be more frequent in younger patients. Of note, in young patients, a muscular deficit could be masked by greater muscle mass, although all CADM patients in our cohort showed CK values within the reference range.

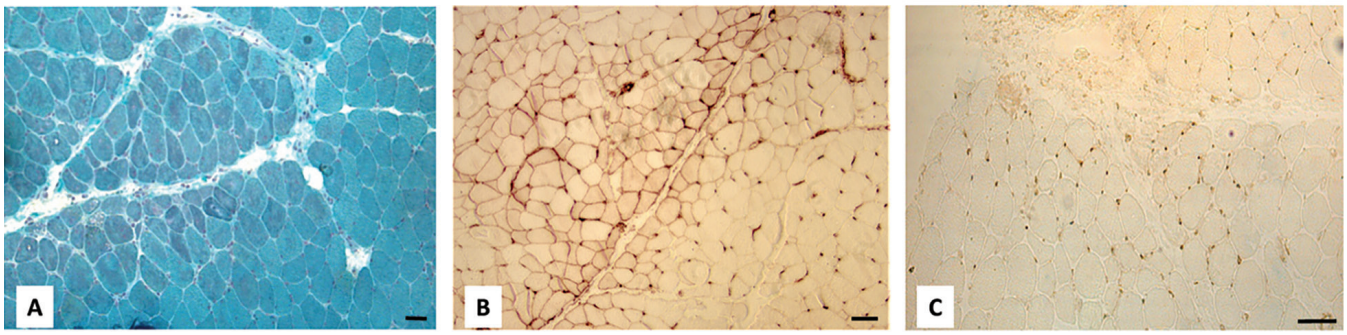

Fig. 2. Representative histopathological characteristics of 3 clinically amyopathic dermatomyositis (CADM) patients. **A**: Perifascicular atrophy and some myofibre degeneration in an anti-SAE1/2 CADM patient; **B**: MHC-I staining with perifascicular reinforcement in an anti-TIF1-γ CADM patient; **C**: MAC deposition on perimysial and perifascicular endomysial capillaries in an anti-MDA5 CADM patient. Scale bars: 50 μm.

Compared to other DM subsets, CADM patients were characterised by a higher prevalence of arthritis and ILD. This finding can be partly explained by the higher prevalence of anti-MDA5 antibodies within CADM group, which are known to be associated with joint and lung involvement (11). In fact, in our cohort, 5 out of 7 patients with ILD and 3 out of 6 patients with arthritis had anti-MDA5 antibodies. Another serological feature we found to be more prevalent in CADM patients was the presence of anti-TIF1γ antibodies, which have also been associated in other cohorts with mild or absent muscle involvement, as well as an increased risk of cancer (2, 12). However, in patients with CADM, we did not observe an increased prevalence of cancer, underscoring the notion that cancer screening should be conducted in all patients with DM, regardless of their clinical presentation or autoantibody profile. Finally, all patients with anti-NXP2 or -Mi-2 antibodies exhibited muscle involvement, which should always be investigated and treated in these subclasses of DM frequently characterised by severe muscle involvement (14, 17, 18).The primary factors affecting prognosis in DM patients, independently from other serological and clinical features, appear to be ILD and cancer, without differences among DM, HDM, and CADM. The latter finding was unexpected as CADM showed a higher prevalence of lung involvement and it might be due to unknown confounding factors or the small sample size.

Of note, according to ACR/EULAR 2017 criteria, patients who do not have a strength deficit can be subclassified as ADM, which also includes patients with HDM. However, patients with HDM may exhibit some muscle abnormalities on laboratory testing that are clinically imperceptible (1, 9). In our work, we have chosen to separate patients with HDM from those with CADM to characterise more precisely the forms of CADM observed in clinical practice, where these patients often do not undergo muscle biopsy. In our patient cohort, 7 out of 16 CADM patients underwent muscle biopsy, and 5 of these 7 showed histological signs of muscle inflammation. Among these, the inflammatory marker detected in all 5 cases was an increase in MHC-I on the sarcolemma of muscle fibres. Elevated MHC-I in muscle fibres is a highly sensitive indicator for myopathy (19, 20). MHC-I usually participates in the antigen presentation process and is generally underexpressed in the sarcoplasm (21), while it is expressed only in endomysial capillaries. In the context of inflammatory processes, such as in IIMs, MHC-I is overexpressed both in sarcoplasm and sarcolemma (20). This overexpression appears to be associated with activation of the NF-kB pathway, increase in pro-inflammatory cytokines and consequent muscle atrophy (21, 23).

According to our findings, pure ADM appears to be an extremely rare entity, as minimal muscle involvement may be present in the majority of DM patients who are clinically or instrumentally negative for myopathy. It should be emphasised that two of the CADM patients who showed no signs of inflammation in muscle biopsy had a condition of CAM. CAM in CADM has been studied in another American patient cohort with a prevalence like ours (14% *vs*. 19%), highlighting that it is characterised by a lower presence of both skin photosensitivity and periungual erythema (24).

Lastly, it is worth noting that HDM seems to be an intermediary phenotype between classic DM and CADM, exhibiting numerous shared clinical and serological characteristics with both.

Our study has some limitations, including the small sample size analysed and its retrospective design, although the data are sourced from a local registry. Moreover, treatment may have halted muscle impairment in CADM patients, although at diagnosis they exhibited no clinical muscle involvement despite a significant diagnostic delay (median 9 months, range 3-14 months), throughout which they received no therapy. Finally, in our CADM cohort, we included patients who may have shown minimal muscle involvement after muscle biopsy. However, our goal was to study a CADM cohort that closely reflects everyday clinical practice, where muscle biopsies are often not performed.

In conclusion, the practical findings of our work are that CADM patients evaluated in everyday clinical practice are those who appear to have a high risk of pulmonary and joint involvement, although many may have subclinical muscle involvement on histology, making pure ADM forms extremely rare.

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