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Dermatomyositis in women: a 15-year retrospective analysis of clinical patterns, malignancy risk, and long-term outcomes at a tertiary center

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Abstract

Introduction: Dermatomyositis is an inflammatory disease that affects the skin and skeletal muscles, with variants including clinically amyopathic dermatomyositis and malignancy-associated dermatomyositis.
Methods: This research analyzes the characteristics of dermatomyositis in women. A retrospective cross-sectional study evaluated clinical presentation, muscle involvement, immunological markers, association with malignancy, complications, and mortality in females during a 15-year follow-up at a tertiary dermatology center.
Results: Thirty women (mean age 63.6 ± 11.6 years) were analyzed. The most common skin manifestations were the V-sign (73.3%), followed by a heliotrope rash and Gottron's papules (70.0% each). Periungual erythema appeared in 50.0%, and the shawl sign in 46.7%. Receiver operating characteristic curve analysis linked the V-sign with age ≥ 62.5 years (area under the curve = 0.75) and periungual erythema with age ≤ 68.5 (area under the curve = 0.76). Muscle weakness was present in 63.3% of cases. Myositis-associated autoantibodies and myositis-specific autoantibodies were positive in 53.3%. Seven patients (23.3%) had malignancy-associated dermatomyositis, including ovarian, breast, endometrial, lung, gastric, and nasopharyngeal cancers.
Conclusions: The V-sign, a heliotrope rash, and Gottron's papules were the most common skin findings. Muscle involvement affected nearly two-thirds of patients. Malignancy was detected in almost a quarter of patients, emphasizing the need for thorough evaluation and early diagnosis, especially in cancer-associated cases.

Keywords: clinical characteristics, dermatomyositis, malignancy, muscle weakness, myopathy

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Introduction

Dermatomyositis (DM) is a rare inflammatory disease that predominantly affects females. The spectrum of clinical manifestations is vast, but skin and skeletal muscles are most involved. However, due to systemic inflammation, vital organs, such as the lungs and heart, can be involved, which significantly affects the mortality rate in DM patients (1). The main variants of DM include classic DM (with skin involvement and proximal skeletal muscle weakness), clinically amyopathic DM (CADM), malignancy-associated dermatomyositis (MADM), and juvenile DM (2). Diagnosing DM requires a comprehensive evaluation of clinical manifestations, immunological analysis with evaluation of myositis-specific autoantibodies (MSAs), imaging techniques like muscle magnetic resonance imaging (MRI), electromyoneurography (EMG), skin, and sometimes even muscle biopsy. Given the strong association with cancer, malignancy screening at diagnosis and periodic follow-ups are crucial for timely intervention and improved patient outcomes (3).

Methods

We conducted a 15-year cross-sectional study involving newly diagnosed female patients with dermatomyositis that were hospitalized, diagnosed, and treated at the female department of a tertiary dermatology center. This study was approved by the Ethics Committee of the University Clinical Center of Serbia, Belgrade, Serbia (no. 307/16). Patients were identified through an international classification of disease (ICD)-10-based search of hospital medical records. The study focused on evaluating initial cutaneous manifestations and the extent of muscle involvement. In cases with suspected myopathy, EMG of the upper and/or lower limbs was performed, and MRI was used when EMG findings were inconclusive.

The diagnosis of DM was established using a combination of clinical, histopathological, laboratory, and immunological criteria. In those patients in whom histopathology was not performed, the diagnosis was made based on pathognomonic clinical manifestations and immunology analysis, specifically MSAs. Myopathy was confirmed through EMG, MRI, and evaluation by a neurologist. Patients without initial signs of myopathy were reassessed for muscle involvement at each subsequent hospital visit. Information obtained from medical records included the patient's age and the interval between symptom onset and confirmation of diagnosis.

Analyzed laboratory data included muscle enzymes at the time of diagnosis, such as creatine phosphokinase (CPK) and lactate dehydrogenase (LDH), as well as antinuclear antibodies (ANA HEp-2), myositis-associated autoantibodies (MAAs), and MSAs. For the detection of ANA HEp-2, MAAs, and MSAs, ELISA kits were used.

All our patients with DM were also screened for malignancy, and we were able to evaluate the association with cancer. The screening included determining levels of specific tumor markers, a Pap smear, a chest X-ray, mammograms, an abdominal ultrasound, a fecal occult blood test (FOBT), and, if indicated, computed tomography (CT) scans and endoscopic procedures. During the follow-up, we also evaluated whether the patients developed

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complications, such as cardiac and lung involvement (myocarditis and arrhythmias, interstitial lung disease, and pneumonia), progressive skeletal muscle weakness and/or oropharyngeal muscle weakness (manifesting as dysphagia), or skin complications such as calcinosis and ulcerations.

Statistical analysis

The Kolmogorov–Smirnov test and Q–Q plots were used to assess the presence or absence of a normal distribution in numerical data. Categorical data are presented as frequencies and percentages (%), and continuous variables are reported as means and standard deviations (*SD*) or medians (with ranges), as appropriate, given the distribution's normality. A receiver operating characteristic (ROC) curve analysis was used to determine the predictive value of the patients' age and clinical manifestation of the disease, and the results are expressed as an odds ratio (OR) with 95% confidence interval (CI). SPSS, version 20.0 (SPSS Inc., Chicago, Illinois, USA) was used for statistical analysis.

Results

This study included 30 females with newly diagnosed DM, with a mean age of 63.6 ± 11.6 years. The median interval between the onset of initial symptoms and the confirmed diagnosis was 6 months (range: 1–84 months).

In all patients, photoexposed areas (face, neck, upper chest, and dorsal aspect of the hands) were affected. The most common skin manifestations were the V-sign, observed in 22 patients (73.3%), followed by a heliotrope rash and Gottron's papules, seen in 21 patients each (70.0%). Gottron's sign was seen in 20 patients (66.7%). Periungual erythema was observed in 15 patients (50.0%). The shawl sign was present in 14 patients (46.7%). Less common skin manifestations included scalp erythema, observed in 10 patients (33.3%), and the holster sign, seen in eight patients (26.7%; Table 1). Histopathology diagnosis confirmation was performed on 26 patients (86.7%).

On the ROC curve analysis, age was statistically significantly associated with the appearance of the V-sign and periungual erythema. Age of ≥ 62.5 years was associated with the presence of the V-sign (area under the ROC curve [AUC] = 0.75, 95% CI = 0.57 – 0.93, $p < 0.05$; sensitivity of 72.7%, and specificity of 75.0%; Fig. 1). Age of ≤ 68.5 years was associated with the presence of periungual erythema (AUC = 0.76, 95% CI = 0.59 – 0.93, $p < 0.05$; sensitivity of 80.0%, and specificity of 60.0%; Fig. 2).

Based on clinical examination, at the time of the diagnosis, muscle weakness was present in 19 patients (63.3%), and 18 of them had EMG findings consistent with myopathy. In seven (23.3%) out of 10 patients that had an MRI, the findings suggested soft-tissue edema and inflammation, which can be seen in dermatomyositis. Other patients did not experience muscle weakness on clinical examination; therefore, EMG and MRI were not performed.

CPK levels were elevated in 16 individuals (53.3%), among whom myositis was confirmed in 11 cases. In addition, LDH levels were elevated in 23 patients (76.7%), among whom myositis was confirmed in 19 cases. Regarding immunology blood analysis, ANA HEp-2 was positive in 23 (76.7%) patients, and 16 patients (53.3%) had positive MAA and/or MSAs at the time of diagnosis (Table 2). MSAs were positive in eight patients (26.7%). For two patients, myositis profiles were not performed due to technical issues. Two patients with confirmed cancer had positive Ro-52 an-

Table 1 | **Frequency of initial clinical manifestations of dermatomyositis in women (*n* = 30).**

Initial clinical manifestations	*n*	%
V-sign	22	73.3
Heliotropic rash	21	70.0
Gottron's papules	21	70.0
Gottron's sign	20	66.7
Periungual erythema	15	50.0
Shawl sign	14	46.7
Scalp erythema	10	33.3
Holster sign	8	26.7

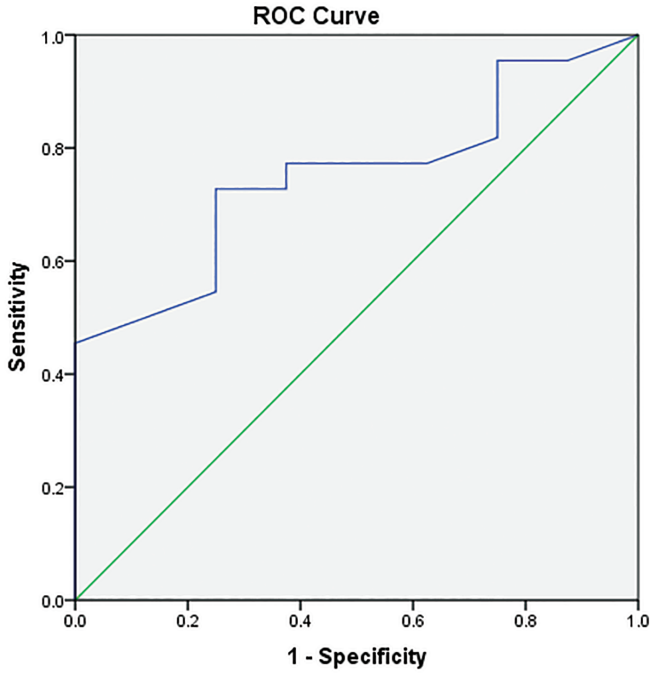

Figure 1 | ROC curve analysis shows that an age of ≥ 62.5 years was associated with the presence of the V-sign (AUC = 0.75, 95% CI = 0.57–0.93, $p < 0.05$; sensitivity of 72.7%, and specificity of 75.0%).
ROC = receiver operating characteristic, AUC = area under the ROC curve, CI = confidence interval.

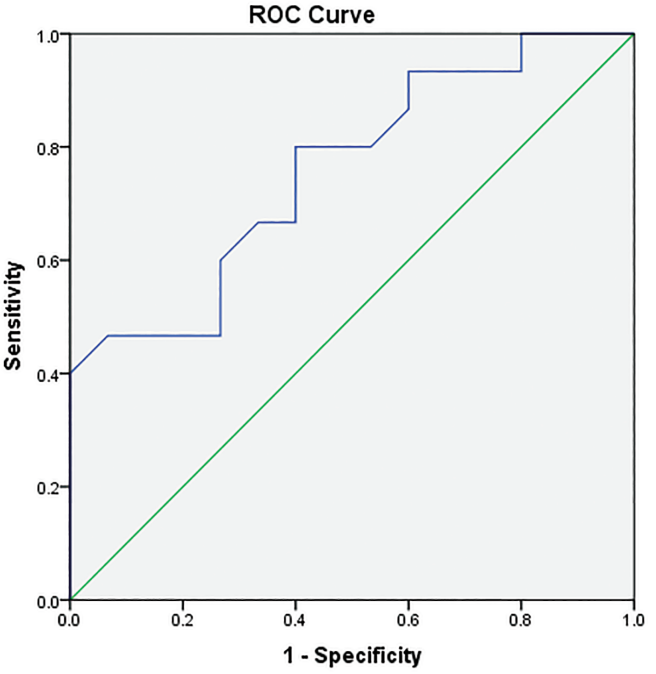

Figure 2 | ROC curve analysis shows that an age of ≤ 68.5 years was associated with the presence of the periungual erythema (AUC = 0.76, 95% CI = 0.59–0.93, $p < 0.05$; sensitivity of 80.0%, and specificity of 60.0%).
ROC = receiver operating characteristic, AUC = area under the ROC curve, CI = confidence interval.

tibodies; one of them also had the anti-polymyositis/scleroderma (anti-PM/Scl)-75 antibody, and the other one had PL-7 positivity; four of them had negative MSAs.

Out of the 11 cases (36.6%) in which the underlying malignant process was highly suspicious, the primary cancer was identified in seven patients (23.3%). Ovarian cancer was diagnosed in two patients; in addition, one case each of breast, endometrial, lung, gastric, and nasopharyngeal cancer was observed (Table 3).

Four patients were lost to follow-up. Out of 26 patients, seven developed complications (26.9%); two patients had pneumonia, four had progression of skeletal myopathy, one of them even developed dysphagia, and one patient had myocardial infarction. Six patients died during the follow-up due to either direct complications of DM or secondary conditions precipitated by the disease.

Discussion

Demographic data

Adult-onset DM is more prevalent in women, with a female-to-male ratio ranging from 2:1 to 4:1 (4, 5). In a study conducted in Minnesota, the patients' mean age was 57 years, and 90% of participants were female (6). Another study from the United Kingdom reported a mean age of 58 years for DM patients, with 66% of the cases being women (1). Our study was conducted in a female department, with a mean age of 63.6 ± 11.6 years among the patients. This further supports the trend of DM occurring in women typically in their 50s and 60s.

Skin manifestations

Skin manifestations are a hallmark of the disease and are important in making the diagnosis, especially in amyopathic forms. A broad spectrum of cutaneous findings can sometimes lead to misdiagnosis, and most commonly can be mistaken for other connective tissue diseases (7). DM-associated cutaneous manifestations can be classified into pathognomonic, characteristic, and compatible lesions based on their diagnostic significance, and additional findings may include rare or nonspecific presentations (8, 9). Pathognomonic cutaneous manifestations of DM include a heliotrope rash, Gottron's papules, and Gottron's sign. Characteristic lesions comprise the shawl sign and V-sign, periungual telangiectasia, and scaly erythematous plaques on the scalp. Compatible findings include poikiloderma and a violaceous or erythematous rash over the lateral aspects of the thighs and hips, known as the holster sign (9, 10). Less common manifestations include flagellate erythema, mechanic's hands, and oral lesions such as an ovoid palatal patch or gingival telangiectasia. Photo-

Table 2 | **Initial findings for positive myositis-associated antibodies and myositis-specific antibodies.**

Patient	MAA	MSA
1	—	anti-Mi-2α +, anti-Mi-2β +
2	anti-PM/Scl-100 +	anti-Mi-2β +
3	anti-PM/Scl-75 +	—
4	anti-Ro-52 +++	—
5	—	anti-Q +, anti-NXP ++
6	anti-Ro 52 +++	anti-TIF1-γ +++
7	—	anti-SAE1 +++, anti-CN1A +++
8	anti-Ro-52 ++	anti-PL-7 ++
9	—	anti-TIF1-γ ++
10	—	anti-PL7 ++, anti-SRP +, anti-TIF1-γ ++
11	anti-Ro-52 ++	—
12	anti-Ro-52 ++	—
13	anti-PM/Scl-75 ++, anti-Ro-52 +	—
14	anti-Ro-52 ++	—
15	anti-Ro-52 ++	—
16	anti-Ro-52 ++	—

MAA = myositis-associated antibodies, MSA = myositis-specific antibodies, anti-PM/Scl = anti-polymyositis/scleroderma, anti-NXP = anti-nuclear matrix protein, anti-TIF1-γ = anti-transcriptional intermediary factor 1-γ, anti-SAE1 = small ubiquitin-like modifier-activating enzyme subunit 1, anti-CN1A = anti-cytosolic 5'-nucleotidase 1A, anti-SRP = anti-signal recognition particle.

Table 3 | Characteristics of patients with malignancy-associated dermatomyositis.

Age of onset	Clinical manifestations	Muscle weakness	Type of cancer	LDH/CPK	MAAs/MSAs
39	Heliotrope rash, V-sign, shawl sign, Gottron's sign, periungual erythema	Yes	Breast	Elevated/ elevated	Negative
60	Gottron's sign, Gottron's papules	No	Ovarian	Elevated/ elevated	anti-PL-7 ++ anti-Ro-52 ++
63	Scalp erythema, heliotrope rash, V-sign, Gottron's sign, Gottron's papules, periungual erythema, holster sign	Yes	Endometrial	Elevated/ elevated	Negative
68	Heliotrope rash, V-sign, shawl sign, Gottron's papules, Gottron's sign, periungual erythema	Yes	Nasopharyngeal	Elevated/ elevated	Not done
71	Scalp erythema, heliotrope rash, V-sign, shawl sign, Gottron's sign, Gottron's papules, periungual erythema	Yes	Ovarian	Elevated/ normal	Negative
75	Heliotrope rash, V-sign	Yes	Lung	Normal/ normal	anti-PM/Scl-75 ++ anti-Ro 52 +
83	Heliotrope rash, V-sign, Gottron's papules, Gottron's sign	No	Gastric	Elevated/ elevated	Negative

MADM = malignancy-associated dermatomyositis, DM = dermatomyositis, LDH = lactate dehydrogenase, CPK = creatine phosphokinase, MAA = myositis-associated antibodies, MSA = myositis-specific antibodies, PM/Scl = anti-polymyositis/scleroderma.

sensitivity and Raynaud's phenomenon may occur but are considered nonspecific features (7, 8, 10).

A 13-year study from tertiary centers in Canada identified Gottron's papules (69%), a heliotrope rash (66%), the V-sign (61%), and the shawl sign (56%) as the most frequent cutaneous findings in DM, with the holster sign and mechanic's hands occurring in 20% and 13% of patients, respectively (5). Data from Colombia revealed lower rates of the V-sign (48%) and shawl sign (30%) (11). Similarly, a Beijing cohort of 64 patients with DM exhibited Gottron's papules, a heliotrope rash, Gottron's sign, and periungual lesions as predominant features, each present in over half of the patients, whereas scalp erythema was noted in one-quarter (12). Our findings mirror these patterns: all patients exhibited involvement of photoexposed areas, with over two-thirds displaying the V-sign, a heliotrope rash, Gottron's papules, and Gottron's sign. Periungual erythema and the shawl sign were observed in about half, and scalp erythema and the holster sign in one-third of patients, corroborating previously reported trends in DM-related skin manifestations.

In our sample, the V-sign was more commonly observed in women older than 62 years (Fig. 1), whereas women younger than 68 were more likely to have periungual erythema (Fig. 2).

Muscle involvement

Muscle weakness is also a common clinical feature of DM, with a significant portion of patients showing signs of myopathy early in the disease course (13). Depending on the presence or absence of clinical muscle weakness, patients are classified as having amyopathic DM (ADM) or hypomyopathic DM (HDM), the latter showing subclinical inflammation on EMG or MRI. Some authors group these under the term CADM. Severe cases may advance to pronounced muscle weakness and substantial functional impairment (14). When assessing muscle involvement, normal CK and LDH levels do not rule out muscle disease, and elevated values do not necessarily indicate its presence. In a study by Volochayev et al., approximately half of patients with DM had elevated CPK and LDH levels, indicating muscle involvement (15). In our research, clinical assessments at the time of diagnosis revealed muscle weakness in more than 60% of patients, and EMG confirmed myopathic changes in nearly all of those affected. MRI performed in a subset of patients consistently indicated soft-tissue edema and inflammation—hallmarks of DM. Elevated muscle enzyme levels, particularly LDH, closely correlated with clinical and EMG evidence of myositis. A comprehensive evaluation, combining clinical assessment, serum enzyme levels, EMG, MRI, and, when necessary, a muscle biopsy, remains essential for an accurate evaluation of muscle involvement in DM.

Immunological findings

MAAs and, more importantly, MSAs play a significant role in the diagnostic algorithm for DM. Recent studies highlight their associations with distinct clinical patterns, muscle involvement, malignancy risk, and disease outcomes (16). Anti-MDA5 antibodies have been linked to more severe systemic inflammation and less favorable prognosis (17, 18), and anti-TIF1-γ antibodies are frequently associated with malignancy (19, 20). Xie et al. observed that "although the difference was not statistically significant, it appeared that patients positive for anti-MDA5 antibodies had a lower survival rate, followed by positive TIF-γ and NXP2 antibodies" (19). The prevalence of MSAs varies widely among populations, with overall positivity rates ranging from 30% to 79% (21, 22).

In our cohort, positivity for MAAs and MSAs was observed at diagnosis, and the rates were influenced by limitations in testing availability. Slightly more than one-quarter of our patients had positive MSAs. Only MAAs were detected in our patients with MADM, which is consistent with findings from a Spanish study on paraneoplastic DM (23). Further research and standardized testing are essential to clarify the clinical relevance of MSAs and improve diagnostic precision and therapeutic management (24).

Association with malignancy

Malignancy can occur before, along with, or following the initial symptoms and signs of DM, and the risk of malignancy for adult DM patients is increased 4.66-fold compared to the general population (3, 25). Based on current data, the incidence of cancer ranges from 7% to 30% in adult patients with DM (26). In a retrospective study conducted in China on 134 patients, 9% were found to have MADM (27). The data from our research suggest a higher prevalence of MADM. Nearly one-quarter of our patients were diagnosed with malignancy, and clinical signs and symptoms of DM were the first manifestations. Having in mind the female predominance in DM, it is not a surprise that gynecological cancers are most prevalent, followed by lung, breast, and colon cancer (28). Our findings align with these trends, showing a similar distribution of associated cancers across gynecologic and other organ systems.

Complications and mortality

Exact information on the prognosis of DM is not fully known because the data in the literature are highly heterogeneous. DM is associated with a range of systemic complications that can significantly impact morbidity and mortality. Multiple factors, such as visceral involvement (interstitial lung disease and myocarditis), progressive muscle weakness that may affect esophageal and respiratory muscles, and association with malignancy, can significantly impact the outcome of DM patients (29). In our study, almost one-third of the patients developed complications; two patients had pneumonia, four had progression of muscle weakness (one of them developed dysphagia), and one patient had myocardial infarction. Six patients died during the follow-up, presumably due to either direct complications of DM or secondary conditions precipitated by the disease, making up a quarter of our adult female DM patients.

Conclusions

In our study, one-quarter of women with DM had an underlying malignancy, and one-quarter died during the follow-up. Therefore, in addition to the importance of malignancy screening in women with a suspicion of DM, our findings also emphasize the importance of regular follow-ups for early detection of disease progression and complications, thereby improving patient outcomes. Comprehensive diagnostics, including the detection of MSAs, are significant for making the diagnosis, and further research is needed to identify the association of specific MSAs with malignancy and complications, allowing us to recognize patients that are at higher risk of a fatal outcome.

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