Amyopathic Necrotizing Dermatomyositis Secondary to an Underlying Malignancy: A Case Report and Review of the Literature

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GOAL

To understand dermatomyositis (DM) to better manage patients with the condition

LEARNING OBJECTIVES

Upon completion of this activity, dermatologists and general practitioners should be able to:

1. Define the diagnostic criteria for classic DM.
2. Differentiate between autoantibodies relevant to classic DM and other variants of the disease.
3. Discuss the relationship between DM and malignancies.

INTENDED AUDIENCE

This CME activity is designed for dermatologists and generalists.

CME Test on page 414.

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We describe a patient with amyopathic dermatomyositis (DM) secondary to an unusual malignancy. Although the association between amyopathic DM and malignancy has been established, our case report is unique in that the patient exhibited necrotic lesions on her skin. Furthermore, histopathologic examination of the skin lesions demonstrated a combination of epidermal findings typical of DM in addition to a necrotizing, paucicellular vasculopathy. The first indication

of an underlying malignancy in this patient was the clinical findings of DM. Prompt identification of such findings may assist in the diagnosis and treatment of the associated malignancy.

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Dermatomyositis (DM) is a rare disorder that typically presents with proximal muscle weakness and a heliotrope rash.[1] Although the exact etiology is unknown, DM is an autoimmune disease.[2] The cause of this autoimmune reaction is unclear, but in adults there often is a notable correlation between DM and the presence of an underlying malignancy.[3,4] Because of its low prevalence and variability in presentation, DM easily can be overlooked or misdiagnosed. In some cases, the cutaneous manifestations of DM may be the first indications of an underlying malignancy, providing an opportunity for early intervention.

We report the case of a woman with an ulceronecrotic form of amyopathic DM associated with an unusual internal malignancy.

Case Report

A 59-year-old woman presented to her primary care physician for a pruritic rash on her arms. The patient was given triamcinolone acetonide cream 0.1%, with no improvement. Over the course of several months, the rash progressed to her chest and trunk, predominately in a sun-exposed distribution. The rash was maculopapular and erythematous, with secondary excoriations. No vesicles, tenderness, or discharge were noted. Lupus erythematosus was suspected, and antinuclear antibody test results were normal at a titer of 1:40 in a homogenous pattern. The patient was given a course of low-dose oral prednisone, which did not alleviate her symptoms.

The patient was referred to a dermatologist. By this time, her rash had progressed further and continued to be pruritic. She developed diffuse, edematous, coalescent papules and plaques on the sun-exposed portions of her chest, back, cheeks, upper and lower extremities, and left buttock. Her fingers were edematous and the cuticles were a deep violaceous color. There were numerous nontender papules on her hands, and she experienced pain upon flexion of the digits.

A punch biopsy specimen from the patient's arm demonstrated nonspecific inflammatory findings suggestive of polymorphous light eruption or drug eruption. Results of a repeat antinuclear antibody test were elevated at a titer of 1:640 in a speckled pattern; however, antibodies to SSA, SSB, DNA, ribonucleic protein (extractable nuclear antigen), Scl-70, and Sm antigens were negative.

The dermatologist prescribed a 3-week tapering dose of oral prednisone. At the patient's next visit, the papules that were previously noted on her hands had become purple and brown and a provisional diagnosis of necrotizing vasculitis was made. Cyclophosphamide 75 mg twice daily was added to the patient's treatment regimen. A second biopsy specimen from the patient's right hand was sent for routine histologic examination as well as direct immunofluorescence. The pathologic interpretation again was nonspecific inflammation of the dermis. Direct immunofluorescence revealed no deposition of IgG, IgM, or IgA; C3; or fibrinogen. Additionally, results of an antineutrophil cytoplasmic antibody test, urinalysis, and metabolic panel were within reference range. Posteroanterior and lateral chest x-rays showed a bilateral hilar prominence that appeared to be vascular, a slight prominence of the pulmonary vasculature, and a prominent azygos vein versus adenopathy.

Over the next few days, the lesions on the patient's hands appeared more necrotic. However, she reported that the higher dose of prednisone and cyclophosphamide prevented new lesions from developing.

The internal medicine department was consulted. Although the patient continued to deny muscle weakness, the internist entertained the possibility of amyopathic DM. The rheumatology department also was consulted and the rheumatologist recommended stopping the cyclophosphamide.

Ten days after the patient's initial chest x-ray, she underwent a computed tomographic scan of the chest, which showed bilateral pulmonary emboli that appeared to be chronic, pulmonary artery dilation to 4.25 cm, left axillary lymphadenopathy, and retroperitoneal lymphadenopathy. She was instructed to go to the closest emergency department and was admitted for further workup. As part of this workup, her lactate dehydrogenase level was found to be 713 U/L (reference range, 100–200 U/L).

After reviewing the patient's history and noting numerous necrotic lesions on the metacarpophalangeal, proximal interphalangeal, and distal interphalangeal joints (Figure 1), as well as lesions near the medial canthus (Figure 2), the dermatologist suspected DM secondary to an underlying malignancy. A biopsy specimen from the left third distal interphalangeal joint showed a paucicellular vacuolar interface dermatitis with scattered necrotic keratinocytes typical of DM (Figure 3). In addition, there was dermal vascular thrombosis with a

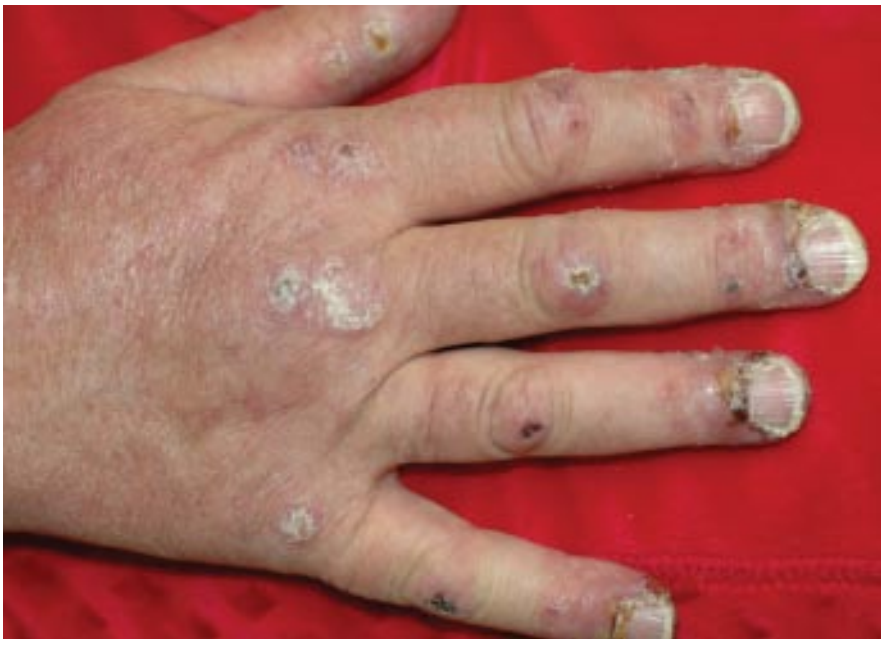

Figure 1. Ulceronecrotic Gottron papules.

focal paucicellular necrotizing vasculopathy. Direct immunofluorescence results were negative. Test results for an underlying malignancy, including carbohydrate antigen 19-9 (CA19-9), cancer antigen 125 (CA125 ovarian cancer marker), carcinoembryonic antigen, hepatitis panel, and human immunodeficiency virus, were all negative. Test results for a hypercoagulable state, including proteins C and S, lupus anticoagulant, anticardiolipin antibodies, and serum and plasma electrophoresis, also were negative.

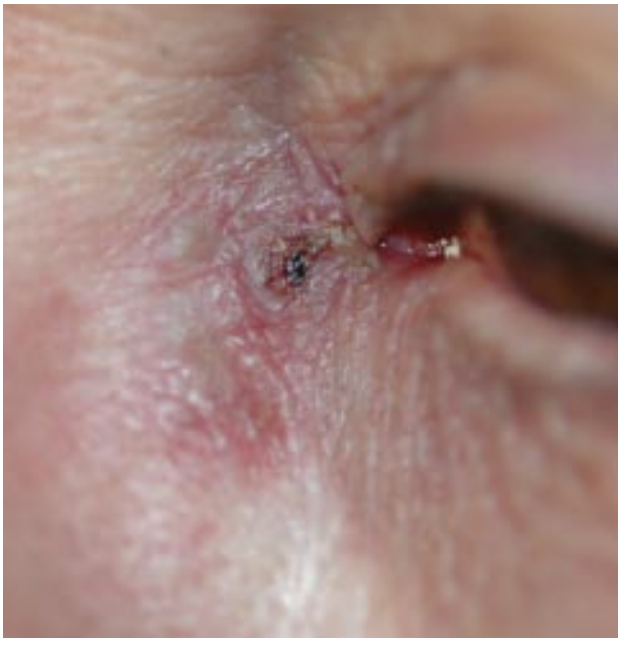

Figure 2. Lesion near the medial canthus that is part of the heliotrope rash found in patients with dermatomyositis.

Subsequently, a biopsy was performed on an abdominal lymph node specimen. The results showed a poorly differentiated malignant neoplasm consistent with small cell carcinoma not of pulmonary origin. Immunohistochemical staining results were positive for cytokeratin AE1/AE3, synaptophysin, neuron-specific enolase, CD117, CD56, CD99, and bcl-2 antibodies. The primary site of involvement could not be identified. Two months after the diagnosis of clinically amyopathic DM (CADM), the patient died of cancer complications.

Comment

Inflammatory myopathies, including DM, are rare disorders, with an estimated prevalence rate of approximately 5.5 per million individuals worldwide.[1] There are several variants of the disease, with different physical examinations and laboratory findings. Classic DM most commonly presents with proximal muscle weakness and an edematous violaceous discoloration (heliotrope rash) around the eyes. Gottron papules (violaceous papules on the metacarpophalangeal, proximal interphalangeal, and distal interphalangeal joints) also may be present in contrast to the lesions of systemic lupus erythematosus, which tend to affect the interphalangeal joints. Diagnostic criteria for classic DM were proposed by Bohan and Peter[5,6] in 1975 (Table).

Patients who present with minimal or no muscle involvement are considered to have hypomyopathic or amyopathic DM. In hypomyopathic DM, the patient does not experience muscle symptoms but has elevated levels of muscle-associated enzymes, such as creatine kinase, aldolase, lactate dehydrogenase, or myoglobin,

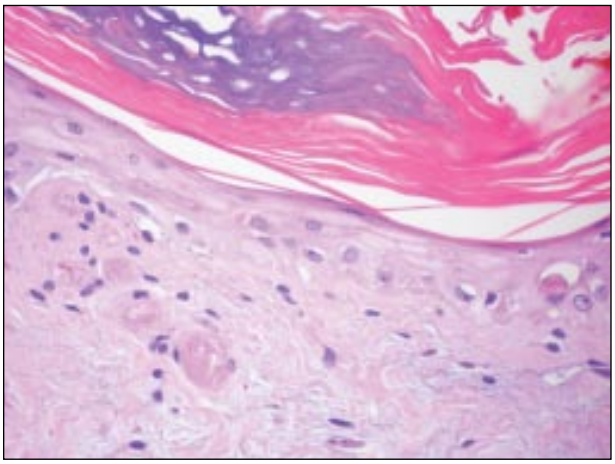

Figure 3. Paucicellular vacuolar interface change at the edge of a cutaneous ulceration (H&E, original magnification ×200).

Diagnostic Criteria for Classic Dermatomyositis[5,6]

- Proximal symmetric muscle weakness
- Elevated serum levels of muscle enzymes
- Abnormal electromyogram result
- Abnormal muscle biopsy result
- Cutaneous disease compatible with dermatomyositis

or an increased urinary creatine to creatinine ratio. As first described by Euwer and Sontheimer,[7] patients with CADM will present with cutaneous manifestations but will not have signs or symptoms of muscle inflammation. Of all patients with DM, CADM represents only 5% to 11% of cases.[7,8]

The underlying pathogenesis of DM is a vasculopathic process,[9] with deposition of the membrane attack complex (MAC) on the endothelium of capillaries in the skin as well as the muscle.[10-12] This process appears to be of an autoimmune nature and involves numerous antibodies directed toward various autoantigens.

Autoantigens and DM—Antinuclear antibody screening commonly is used to detect autoimmune diseases such as DM. Although this test may yield a positive result, typically in a speckled pattern, one-third to one-half of patients with DM will have a negative antinuclear antibody test result.[1,13] Myositis-specific antibodies (MSAs) may assist in the diagnosis of DM and also can help in prognostic and treatment decisions. Antisynthetases, a subset of MSAs, have targets in the cytoplasm of cells. One target is an antibody to Jo-1, also known as histidyl–transfer RNA synthetase, which is present in 80% of patients with DM with an antisynthetase antibody.[14] The significance of this antibody is yet to be fully elucidated, but its presence appears to correlate with muscle weakness, Raynaud phenomenon, and nonerosive arthritis. Interestingly, the Jo-1 autoantigen shares structural homology with the picornavirus, which is known to cause myositis.[15] Furthermore, increased concentrations of native Jo-1 in the body will not induce an immune response, but recombinant Jo-1 from patients with DM will induce the proliferation of HLA class II antigen–restricted peripheral T cells, meaning that Jo-1 must somehow be modified before becoming an autoantigen.[16,17]

The presence of any of the antisynthetase antibodies (Jo-1, PL-7, PL-12, OJ, EJ) can lead to the antisynthetase syndrome. Anti–Jo-1 is the most common and is associated with 60% to 80% of all cases of the antisynthetase syndrome.[15] Patients with this syndrome have a poor prognosis compared with other patients with DM because they are more susceptible to interstitial lung disease and tend to respond poorly to therapy.[1] Overall, the mortality rate of these patients is 3 times that of other patients with DM. However, the malignancy rate in these patients tends to mirror the general population rate,[15] which is unusual considering that the estimated rate of malignancy in patients with DM is 50%.[18] In other words, antisynthetase syndrome appears to lack an association with malignancy. Patients with antisynthetase syndrome tend to have only one specific MSA, but they may have other antibodies known as myositis-associated antibodies.[15]

Besides antisynthetases, there are other important MSAs that can influence prognosis and treatment response and may indicate the presence of an associated malignancy. The most specific MSA for DM is anti–Mi-2 whose target is a nuclear helicase. Ninety-seven percent of patients who test positive for the Mi-2 antibody have DM.[15] In general, these patients have a better prognosis than patients with antisynthetase syndrome because interstitial lung disease and coexisting neoplasms are less common compared with all patients with DM.[15] However, cutaneous findings are more common.[19]

A study from Japan found an antibody that reacted against a 140 kDa peptide (anti–CADM-140) that was present in 8 of 15 individuals with CADM.

Although there was lesser severity of muscle involvement in this subset of patients, it appears that the anti–CADM-140 MSA is a marker for more aggressive interstitial lung disease.[20] Kaji et al[19] described another autoantibody that reacted against both a 155 kDa and a 140 kDa peptide (anti-155/140 antibody). Among 52 patients with DM, 7 (13%) patients had this antibody. The anti-155/140 antibody compared with DM controls without this autoantibody (n=45) correlated well with the presence of Gottron papules (100% [7/7] vs 58% [26/45], respectively; $P<.05$), a heliotrope rash (86% [6/7] vs 38% [17/45], respectively; $P<.05$), and most significantly flagellate erythema (86% [6/7] vs 20% [9/45], respectively; $P<.005$). Unlike anti–CADM-140, this autoantibody lacks the association with aggressive interstitial lung disease. However, the anti-155/140 antibody seemed to indicate the presence of an underlying malignancy (71% [5/7] of patients with anti-155/140 antibody vs 11% [5/45] without the antibody).[19]

Specifically for CADM, it appears that there is another autoantibody that reacts against a 155 kDa autoantigen. Similar to the anti–CADM-140 autoantibody, the presence of this anti-155 autoantibody appears to be highly correlated with CADM and rarely with classic DM.[1,15,20]

Clearly, in DM there are autoantibodies that react against both endomysial and skin capillaries, causing the clinical features of the disease. The end result of the interaction between autoantibodies and antigens in these capillaries is the activation of the complement cascade.[1,2,14] The process begins with the activation of C3 and ends with the formation of the MAC, C5b-9, which causes lysis of these capillaries.[21] This lysis causes microinfarcts and hypoperfusion of the involved tissues, causing muscle weakness and/or cutaneous lesions. However, MAC, C3b, and C4b have been detected on the capillary walls of patients before they had clinically significant disease.[12,14] In one study of 22 skin biopsy specimens taken from patients with DM, depositions of MAC were found at the dermoepidermal junction in 86% (19/22) of biopsy specimens and on the endothelium of dermal capillaries in 77% (17/22) of biopsy specimens.[11] The repeated lysis of capillaries over time leads to a decrease in the number of capillaries, which is a common finding on biopsy of both muscle and skin specimens.[22] Dermatomyositis muscle biopsy results commonly show fibrin thrombi inside of endomysial capillaries leading to microinfarcts of portions of the fascicles or the periphery, resulting in perifascicular atrophy. This histologic finding is diagnostic for DM, even in the absence of inflammation.[14]

Our patient demonstrated a dramatic thrombotic and focally necrotic vasculopathy that is unusual for DM or CADM but has been previously reported in both.[9,23] However, necrotic vasculopathy may not always be associated with an underlying malignancy. In fact, one study found that of 30 patients with both DM and a malignancy, only 2 had necrotic lesions on their body.[24]

Malignancy and DM—It has been proposed that there is a notable correlation between DM and the presence of an underlying malignancy[4,14,18,25-28]; patients with DM have a higher risk of dying from a malignancy than the general population.[3] Studies have placed the co-prevalence of DM and cancer at 20% to 30%.[29,30] In retrospective studies only, patients with DM have been compared with healthy cohorts to calculate a standardized incidence ratio (SIR) for the occurrence of malignancies in both groups. The SIR for all cancers in groups of patients with DM has been found to be 3.0 to 7.7 ($P<.05$). This correlation does not appear to be as prominent in other myositides.[4,18,27,28]

The cause-and-effect relationship between DM and cancer also is unclear, as patients have been diagnosed with malignancies both before and after they were diagnosed with DM.[4,18] Other confounding variables, such as poor detection methods for occult malignancies, an immunocompromised state, and the use of immunomodulatory drugs to treat DM,[26,28,30,31] make it even more difficult to ascertain if DM causes malignancies or vice versa. In one study of 618 patients with DM, 198 patients had cancer, of which 115 patients developed cancer after being diagnosed with DM, suggesting that DM is a risk factor for developing cancer.[4] However, other studies have found that the severity of a patient's DM will decrease if their malignancy is surgically removed[29,31] and exacerbations of DM could be used to gauge recurrences of a malignancy,[29] indicating that DM is a paraneoplastic process that occurs after the malignancy has emerged. Thus, it is possible that the temporal relationship of the diagnoses of DM and cancer exists as it does because the first clinical findings are those of DM, prompting the patient to seek care.

Some authors believe there is no connection between the two, claiming that the increased incidence of cancer in patients with DM is due to increased vigilance, leading to detection bias, which is indicated by the disparity in the SIR of cancer between the first year of diagnosis of DM and subsequent years. In one study, the SIR for cancer during the first year after diagnosis of DM was 26 (95% confidence interval [CI], 12-48).[27] Another study noted a relatively high SIR for cancer during

the first year after diagnosis but then a slow decrease in incidence in the following years.[28] Some researchers believe it is a self-perpetuating phenomenon; that is, clinicians who believe there is an increased risk for malignancy will conduct a more thorough cancer workup in their patients with DM and therefore will find more malignancies.[28,32] Also, many of the studies previously mentioned here were retrospective, so the case controls likely did not undergo the same extensive cancer workups as the participants with DM. There is at least one study reporting that there is no link between DM and cancer,[32] but this study involved smaller patient populations and combined patients with polymyositis and DM into one cohort. This combination would have the effect of diluting the incidence of malignancy because patients with polymyositis do not have the same risk for malignancy as patients with DM.[3,14,27]

A valid association between DM and cancer is supported by the fact that when a malignancy is found, it tends to be one of a subset of cancers. Lymphoma, ovarian, lung, and pancreatic malignancies dominate this subset.[3,4,14,28] While ovarian cancer is only the sixth most common malignancy among females in the United States,[33] studies have determined the SIR for ovarian cancer in a group of patients with DM was between 10.5 (95% CI, 6.1-18.1) and 15.5 (95% CI, 4.2-39.8) compared with case controls.[4,28] During the first year of disease, the SIR for ovarian cancer in this same group was 38.2 (95% CI, 10.8-102.4).[28] In most cases of ovarian cancer, the clinical features of DM were recognized before the cancer.[34] If DM can be recognized early, it may allow for timely intervention and cure of a potentially lethal disease.

Conclusion

This case report describes a patient with CADM and an internal malignancy, a known association.[8,13,35,36] However, at least 2 studies have shown a lack of malignancies in CADM, particularly in white patients.[37,38] To our knowledge, this case report of CADM is the first association with a poorly differentiated, nonpulmonary, small cell carcinoma, and only the second report of a patient with CADM secondary to a malignancy with necrotic DM lesions of the skin.[39] In addition, the histologic association of prominent vasculopathic changes with vacuolar interface dermatitis is unusual, and in our case, it resulted in a delay in histologic diagnosis.

There is no established clinical presentation of DM or CADM that is pathognomonic for the presence of an underlying malignancy. There must be a high degree of suspicion of cancer in any patient presenting with the signs or symptoms of either DM or CADM. On diagnosis of DM or CADM, a workup to include breast, colon, and pelvic examinations; complete blood cell count; liver function enzyme and stool guaiac tests; urinalysis; and chest x-rays are indicated. For females, a CA125 test to screen for ovarian cancer also is indicated.[13]

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