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ORIGINAL ARTICLE

How can we effectively address the paraneoplastic dermatomyositis: Diagnosis, risk factors and treatment options

Ioannis Zerdes[1]*, Maria Tolia[2]*, Michail Nikolaou[3], Nikolaos Tsoukalas[4], Louloudenia Velentza[5], Jiannis Hajiioannou[6], Michail Mitsis[7], George Kyrgias[2]

[1]University of Ioannina, School of Health Sciences, Faculty of Medicine, Ioannina, Greece; [2]University of Thessaly, School of Health Sciences, Faculty of Medicine, Radiotherapy Department, Larissa, Greece; [3]Hippokration University Hospital of Athens, Oncology Clinic, Athens, Greece; [4]Veterans Hospital (NIMTS), Oncology Department, Athens Greece; [5]University of Thessaly, School of Health Sciences, Faculty of Medicine, Larissa, Greece; [6]University of Thessaly, School of Health Sciences, Faculty of Medicine, Department of Otolaryngology, Larissa, Greece; [7]University of Ioannina, School of Health Sciences, Faculty of Medicine, Department of Surgery, Ioannina, Greece

*These authors contributed equally to this study

Summary

Purpose: *Dermatomyositis (DM) represents an auto-immune inflammatory myopathy. In this review, we analyzed the incidence of DM as a clinical manifestation highlighting the peculiar clinical and treatment characteristics of this disease when occurring in the context of different malignancies.*

Methods: *A systematic literature review was performed based on database search in PubMed/Medline and included English articles until December 2016.*

Results: *In up to 20% of cases DM appears as a paraneoplastic syndrome associated with multiple malignancies such as ovarian, breast, prostate, lung, nasopharyngeal and colorectal cancer, and non-Hodgkin lymphomas. It can be presented either before, in the time, or after cancer diagnosis. Systemic sclerosis and mixed connective-tissue disease represent common coinciding disorders. Particular caution should be given in the radiotherapy because the microvascular endothelial radiation damage and autoimmune inflammatory collagen vascular disease caused by DM may be additive. There is a higher risk of late toxicity in the presence of other concurrent vascular diseases, including diabetes, hypertension or administration of chemotherapy. Prednisone represents the first-line treatment option but immunosuppressive drugs such as azathioprine and methotrexate may also be incorporated in the therapeutic armamentarium especially when DM is associated with malignancy. Intravenous immunoglobulin could be a promising alternative in prednisone-resistant cases. The effectiveness of therapies with antigen-specific agents such as monoclonal antibodies is currently under investigation.*

Conclusions: *Timely diagnosis coupled with a treatment plan focused on muscular endurance and improvement of skin lesions and other symptoms offer a favorable response to therapy along with the achievement of a higher quality of life for these patients.*

Key words: *dermatomyositis, paraneoplastic syndromes*

Introduction

DM belongs to a heterogeneous group of connective-tissue diseases called idiopathic inflammatory myopathies (IIMs) [1]. This clinical entity mainly presents with proximal skeletal muscle weakness and inflammation as well as with skin manifestations. DM affects almost 10 cases per million, with a peak incidence observed between 50-60 years of age. It can occur in both adults and

Correspondence to: Maria Tolia, MD, Msc, PhD. University of Thessaly, School of Health Sciences, Faculty of Medicine, Radiotherapy Department, Biopolis, 411 10 Larissa, Greece.
Tel: +30 6945472195, +30 2413502054, E-mail: mariatolia@med.uth.gr
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children with a female predisposition (female/male=2:1) [2]. The pathogenic mechanism of the disease includes inflammatory reaction with mediation of B-lymphocytes and CD4+ T-lymphocytes, presence of the complement C5b-9 membrane attack complex (MAC) and antibodies in muscle capillaries. The association of DM with malignancy was firstly described in 1916, in a case of patient with DM who presented with gastric cancer. Thereafter the increased risk of underlying malignancy in patients with DM was elucidated and supported by large retrospective case studies and population-based studies. Malignancy was found to be correlated with DM in approximately 24% of the cases, when based on retrospective case series [3]. Regarding population-based studies from different countries an increased risk of malignancy in DM was indicated with standardized incidence ratios to range from 3.8 to 7.7 [4-9]. A wide variety of types of malignancies has been described to be linked with DM and there is a deviation based mainly on patient's ethnicity. Thus, the spectrum of DM-associated malignancies resembles this of the general population with the most common cancers to include ovarian, lung, gastrointestinal, breast and non-Hodgkin lymphomas [8-13]. Among Asian patients, nasopharyngeal cancer has been reported to be the most common malignancy [14,15]. Adenocarcinoma is the most frequent histological subtype representing 70% of the reported tumors [11]. Although the exact etiology of cancer-associated myositis remains obscure, there are many proposed theories to explain the above condition. Some of them include: i) the paraneoplastic nature of DM through tumor-produced mediators, ii) shared environmental factors which induced autoimmune reactions or iii) malignant transformation triggered by agents for DM management [16].

Diagnostic evaluation, risk factors and treatment options of cancer-associated DM are the main areas that are going to be covered later in this manuscript.

Methods

A systematic literature review was performed based on database search in PubMed/MEDLINE and included articles up to December 2016. The terms used for the search were 'Paraneoplastic Dermatomyositis, 'Cancer', 'Diagnosis', 'Risk Factors', 'Treatment', and synonyms combined with one or more of the following: 'malignancy'. Furthermore, these terms were combined with the respective key words for each paragraph. Publications mentioned in the reference list found in the database search and considered suitable were manually searched for. Clinical phase I, II, randomized phase III and IV studies, reviews, meta-analyses and abstracts of important meetings were analyzed. Only articles published in English were included.

Results

Diagnosis

Many attempts have been made to establish diagnostic criteria for DM. The majority of them are deficient in terms of validity. The most known and widely used are those described by Bohan and Peter in 1975 and 4 out of 5 criteria refer to muscle involvement [17]. According to the authors a) weakness, b) laboratory examinations with increased serum muscle enzymes levels, c) abnormal findings in electromyogram (EMG) indicating myopathy, d) pathologic evaluation of muscle biopsy material are crucial for the establishment of DM diagnosis, e) cutaneous manifestations. According to the aforementioned criteria, the diagnosis of DM is definite when the cutaneous rash is present and 3 or more of the other criteria are fulfilled. If the characteristic rash is not present but there are the typical muscle biopsy findings, DM is characterized as possible. When the skin rash is present on the absence of muscle weakness, the diagnosed disease is called amyopathic DM [18].

i) Clinical criteria

DM is characterized by a wide range of clinical manifestations extended to multi-organ involvement. Predominant is a slow processing, gradual muscle weakness ranging from mild to severe gravity with atrophy. DM is usually symmetric and proximal, affecting mainly the deltoids and hip flexors. The patients complain for impairment in their everyday physical activities (i.e. climbing stairs, picking up weight) [19].

As far the skin changes are concerned, characteristic is heliotrope periorbital rash (an erythematous to blue-purple eruption) on the upper eyelids, sometimes accompanied with edema. Gottron's papules are violaceous papules located in the knuckles especially in the metacarpophalangeal and interphalangeal joints. Poikiloderma with a diffuse erythematous rash on the face-neck and on the anterior surface of the chest (V sign) or on the back (shawl sign) can also occur in DM patients [1,18].

Extramuscular manifestations include dysphagia due to the weakness of esophagus and oropharyngeal muscles [20], cardiac involvement in the form of arrhythmias, myocarditis and heart failure [21] while subcutaneous calcifications can be seen in some patients especially in elbows and back. Lung can be also affected with interstitial

lung disease and respiratory insufficiency to occur due to the weakness of thoracic respiratory muscles, mainly in patients with antisynthetase antibodies [19].

ii) Laboratory testing

Elevation of serum muscle enzymes is of high importance in the diagnostic assessment. Creatine kinase (CK), lactate dehydrogenase (LDH), aldolase and aspartate and alanine aminostranferases are increased in patients with DM and other idiopathic inflammatory myopathies [22]. In patients with active disease, CK serum concentration can be elevated up to 50 times with the CK levels to be usually correlated to the severity of the disease. In some cases of early disease, CK levels can be increased without signs of muscle weakness [18].

iii) Electromyography (EMG)

EMG is helpful in supporting the diagnosis of DM, distinguishing IIMs from other neuropathies. Abnormalities such as increased spontaneous activity with fibrillations, repetitive discharges of high complexity and positive sharp waves can be detected through EMG evaluation. But these charges are non-specific of IIMs and EMG can be normal in some patients [23,24].

iv) Muscle imaging

Magnetic resonance imaging (MRI) and/or computed tomography (CT) can be useful either in confirming the diagnosis of DM or indicating the appropriate muscle for biopsy. CT is better for detection of subcutaneous calcifications and should be performed in cases of pulmonary symptoms and of high suspicion of interstitial lung disease (ILD) along with pulmonary function tests. MRI remains the method of choice for recognizing muscle inflammation, edema and calcifications indicative of muscle myositis. Characteristic is a diffuse protype of high signal intensity on T2-weighted fat-suppressive (STIR) images and high intensity in T1, T2-weighted images when muscle atrophy is pointed as the disease progresses [25].

v) Muscle biopsy

Histopathologic evaluation of muscle biopsy is the cornerstone in diagnostic confirmation of DM, and if feasible, should be performed before any treatment. The biopsy must be performed in muscles with weakness but not atrophical, preferably from deltoids or quadriceps. When a previous EMG testing was done, the contralateral muscle is preferred for biopsy [24]. Alternatively, muscle selection is based on MRI abnormal findings.

The characteristic features present in muscle biopsy that indicate DM include: inflammation of perivascular and perifascicular regions along with atrophy as well as necrosis of muscle fibers. Reduction of capillary density can also occur due to endothelial hyperplasia. Inflammatory infiltration by CD4+ cells (dendritic and T-cells), macrophages and B cells can be observed in perimysial septae [18]. Also, the presence of the complement C5b-9 membrane attack complex (MAC) and antibodies in muscle capillaries can be detected [26]. Perivascular infiltration by lymphocytes can be also detected in the dermis along with epidermal atrophy when biopsy of DM skin manifestations is taken and examined on light microscopy.

Evaluation and screening for malignancy in DM patients

The diagnosis of malignancy can be set before, at the same time or after the onset of DM [6,27]. The risk of cancer is greater during the first year after DM diagnosis (60-70%) and there is a gradual decrease the following years. The time range of cancer risk is generally 2 years before and 3 years after the DM recognition [28]. Thus, especially for DM, the risk of certain types of malignancies (i.e. colorectal and pancreatic cancer) is possible up to 5 years after DM emergence [11].

Due to the association of DM and cancer, it is of high importance for DM patients to be properly evaluated for the presence of an underlying malignancy. Especially for DM patients over 50 years of age, detailed history and physical examination in an annual basis should be performed as well as routine laboratory tests such as complete blood count (CBC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), metabolic profile testing and urine analysis. Apart from these studies DM patients should undergo further diagnostic examinations related to age and gender factors. Screening colonoscopy in all patients over 50 years of age and (if not indicated- fecal occult blood test) and chest radiograph should be performed. For men, screening should be focused on prostatic and testicular examination and for women, pelvic and transvaginal ultrasound, mammography along with Pap-test should be undertaken [3,29].

Further diagnostic evaluation with CT of the chest, abdomen or pelvis should be performed in case of presence of abnormal signs in the previous screening tests or in patients with risk factors for occult malignancy (i.e. family history, smokers, racial factors). Specifically for Asian patients, thorough examination should be done for the presence

of nasopharyngeal cancer while in DM patients with dysphagia the possibility of esophageal cancer should be excluded.

Although whole body positron emission tomography / CT (PET/CT) is a really useful technique for assessing malignancy, its value in screening DM patients for occult malignancy seems not to be more beneficial compared to screening with CT [29,30]. Additionally, general blind test for DM-associated cancer is not recommended regarding the high cost and time-spending procedure [31].

Risk factors

Recognizing DM patients for occult malignancy is of great importance because this group of patients will gain benefit both from a thorough screening which will enable earlier cancer detection and from the respective anticancer treatment. There is a variety of factors associated with lower and higher frequency of underlying malignancy in patients diagnosed with DM. These include clinical and laboratory risk factors correlated with positive or negative cancer risk. Older age at the time of DM diagnosis and male sex seem to be associated with a higher risk for hidden malignancy. In 4 population-based studies the age limits at risk range from 40 to 74 years of age in DM patients [4,6,7,9]. In a multivariate analysis of 121 patients with DM, the mean age of great cancer risk was 52 years [32]. Regarding DM manifestations, more severe presentation of the disease, especially involving muscle and skin, is correlated with a higher risk of underlying malignancy [33]. Severe distal muscle weakness, respiratory muscle involvement leading to respiratory insufficiency and dysphagia are among positive cancer risk factors in these patients [28]. Skin findings such as leukocytoclastic vasculitis, cutaneous necrosis, periungual erythema, ulceration and V or shawl sigh are linked with cancer emergence [28,34]. On the contrary, signs of overlap syndromes' presence such as collagen disorders, seem to have a protective role against malignancy. These include interstitial lung disease (ILD), Raynaud's phenomenon, arthritis or joint involvement and fever, while a higher cancer risk has also been pointed in cases of refractory and recurrent DM [6,28]. Laboratory findings can provide indications regarding the possibility of malignant disease. ESR and CRP are elevated in DM patients with underlying cancer [35,36]. In these patients CK and LDH serum levels are lower compared to DM patients without malignancy or even in normal ranges [33,37], although it is not uncommon for the reverse phenomenon to be seen. Furthermore/moreover low levels of complement 3 (C3) and 4 (C4) and tumor marker elevation are linked with higher cancer possibility while high titters of anti-nuclear antibodies and lymphopenia (<1500/mm^3) are correlated with lower frequency of DM-associated malignancy [3,32,38]. There are some autoantibodies detected in the serum of DM patients which provide either positive or negative risk for an occult malignancy. On the other hand, myositis-specific antibodies such as anti-synthetase antibodies, anti-Jo-1, anti-Mi-2 and anti-SRP along with myositis-associated antibodies such as anti-RNP, anti-PM-Scl and anti-KU confer a protective role, decreasing malignancy risk in DM patients [27]. On the other hand, the antibody against 155 and 140 kD nuclear proteins (anti-p155, anti-p155/140) is associated with positive cancer risk [39]. The p155/140 antibody against the transcriptional intermediatory factor 1-gamma (TIF1-γ) leads to regulation of transforming growth factor β (TGFβ) having an impact on the pathogenic procedure of cancer and autoimmune disorders [3].

Treatment options

Treating patients with DM remains a difficult issue especially when an underlying malignancy is present. We will refer over the current therapeutic strategies in DM as well as to the clinical course of DM after cancer treatment. The ultimate targets of DM therapy are to help patients in terms of muscle strength improvement, to alleviate the skin symptoms and to properly handle the extramuscular manifestations. These goals are not usually easy-to-achieve due to the frequent disease recurrences and relapses or to DM therapeutic resistance. Therefore, it is important therapy to be tailored according to each patient's disease severity, comorbidities, risk factors and drug safety profile.

i) Initial treatment

Corticosteroids

The gold standard in the therapeutic management of DM are corticosteroids, and unless there is no evidence of their effectiveness in prospective randomized clinical trials, corticosteroids seem to offer better results in muscle strength and function improvement [40]. Although their administration is empirical, general recommendations indicate that patients should be initiated with prednisone at a daily dose of 1mg/kg (maximum dose 80-100 mg/day) for 4-6 weeks [18,40]. Higher corticosteroids doses should not be encouraged due to their side effects [25]. The majority of pa-

tients are expected to respond to this kind of therapy with a complete or partial disease remission. Assessment of response to treatment is really important and should be done periodically after treatment initiation. Clinical examination of possible muscle strength improvement which may be slow and gradual along with serum muscle levels concentrations are the major elements of treatment evaluation. CK is expected to be decreased in approximately 2 weeks after treatment onset while normal levels will be pointed long after [41]. Therapeutic effects should be pursued regarding clinical improvement and not normalization of CK levels, because the latter can lead to overtreatment [18]. After a time period of 4-6 weeks prednisone should be tapered. Dose should be decreased by 10 mg every week until a 40 mg/day dose is reached while after this dose, a weekly decrease by 5 mg, 2.5 mg and 1 mg until finally a 5 mg/ day to be reached [42]. This practice can be changed in cases of disease relapses and as a result patients should be monitored closely.

When, despite glucocorticoid administration muscle weakness persists, there are some possible conditions that should be excluded before thinking about other lines of therapy. These include steroid-induced myopathy, other neuromuscular diseases and the presence of occult malignancy. It is a common side effect of corticosteroids induced-myopathy that affects mainly the proximal lower muscles. In this case the CK serum levels are low or normal as the muscle weakness exists or progresses. EMG and/or MRI tests should be performed again while reduction of the prednisone will lead to improvement of muscle strength [25]. Muscle biopsies may be repeated when other diagnosis such as inclusion body myositis (IBM) or dystrophy are under suspicion [41]. Underlying malignancy should always be kept in mind and the screening procedure was referred previously. If the above mentioned conditions are excluded, there are strong possibilities for disease flares or steroid-refractory cases which will alter the therapeutic landscape in this setting of DM.

ii) Recurrent and resistant disease

Immunosuppressive drugs

Azathioprine usage has shown effectiveness in the treatment of patients with DM [43]. In clinical practice it can be used in combination with prednisone as initial therapy, especially in patients with severe disease or many comorbidities. Many clinicians use azathioprine as second-line treatment for steroid-refractory cases. A randomized controlled trial compared prednisone plus azathioprine versus prednisone plus placebo, and showed better outcomes in the combination arm [44]. Azathioprine can be initiated at a dose of 50 mg/day orally with a maximum dose of 2.5-3 mg/kg/day after an increase of 50 mg every 2 weeks, while it usually takes 4-6 weeks for azathioprine to work and for a response to be seen [42]. CBC should be performed so as the patients to be monitored, as the adverse events include bone marrow suppression, hepatotoxicity, pancreatitis, teratogenicity and high risk of carcinogenicity [41]. Systemic reaction characterized by fever, nausea and gastrointestinal symptoms occurs in 12% of the patients and can lead to therapy discontinuation [45].

Another glucocorticoid-sparing drug that is used to refractory cases is methotrexate (MTX). No prospective controlled studies are available for assessing MTX in DM and data for responsiveness to this drug stem from retrospective studies [43,46]. MTX is administered orally one time a week at an initial dose of 15 mg/week to up to 25mg/week (after increase of 2.5 mg/week). If at this maximum dose no response is observed, a dose increase is recommended but the way of administration turns to parenteral. Adverse events of MTX include alopecia, stomatitis, teratogenicity, leukopenia, gastrointestinal symptoms as well as interstitial lung disease and pulmonary fibrosis [41,42]. Due to the latter effects, MTX should be avoided in DM patients with extramuscular manifestation of ILD and in patients with anti-Jo-1 antibodies. Close monitoring with CBC, liver tests and pulmonary function tests should be performed while the risk of side effects can be reduced with simultaneous administration of folinic acid. Its safety profile and frequency of intake offer advantage against azathioprine, though when compared in a double-blind trial the two drugs showed same efficacy [47].

Cyclophosphamide seems to have mixed results when used orally or intravenously in DM patients [48,49] at a dose of 1-2 mg/kg/day and 0.5-1 g/m^2/month respectively [42]. Among the adverse events are gastrointestinal complaints, bone marrow toxicity and hemorrhagic gastritis while the risk of developing cancer is high.

Cyclosporine and tacrolimus have been shown their efficacy in DM patients but their high cost and adverse events such as hypertension, renal toxicity and gastrointestinal symptoms restrict their usage [50,51]. Along with cyclophosphamide, cyclosporine and tacrolimus should be used in cases of steroid failure and when other immunosuppressive agents were unsuccessfully tried.

Mycophenolate mofetil seems to be a prom-

ising drug in the management of patients with resistant DM [52-54]. Common adverse events include diarrhea, fever, nausea and leukopenia while a high risk for opportunistic infections accompany its use [55,56]. It is not clear if it is superior to other immunosuppressive drugs but its safety profile (no liver or renal toxicity) make it a possible effective agent in the therapeutic armamentarium.

Other therapies

Intravenous immunoglobin (IVIG) is an effective second-line therapy for refractory DM cases. A double-blind cross over placebo controlled trial of 15 patients treated with IVIG infusions after prednisone, showed clinical improvement in muscle strength [57]. Adverse events include: nausea, chills (flu-like symptoms), rash, myocardial infraction and aseptic meningitis [42].

Rituximab, the anti-CD20 monoclonal antibody, is promising and effective as a second-line glucocorticoid-sparing agent, although the RIM (Rituximab in Myositis) trial demonstrated no differences in response to early or late rituximab administration [58].

iii) Management of extramuscular disease

Due to the multisystemic involvement in DM, it is important for patients to be helped and confront the severe consequences of disease progression. The role of exercise is important in empowering patients' musclular condition or improving endurance although there are no studies available to confirm benefit. It should be initiated even from the early stages of the disease with variable types and intensity depending on the patients' status and loss of weakness [59]. Patients suffering from dysphagia will need consultation from a speech therapist. As the risk of aspiration is high due to the inflammation of cricopharyngeal or muscles of the esophagus, proper measurements should be adopted to reduce this hazard. Maneuvers, food in liquid form or in small pieces or even a feeding tube will be useful in these patients. Due to the usage of high-dose corticosteroids and other immunosuppressive drugs, patients treated may suffer from various side effects. Steroid-induced osteoporosis is a common problem and patients should take prophylactic calcium supplementation and vitamin D [42]. Another major effect is opportunistic infections. Especially in patients with ILD, apart from fungal and mycobacterial infections, pneumocystis jirovecii can cause serious problems. For that reason, prophylaxis with trimethoprim-sulfamethoxazole should be administered in these patients [41].

iv) Factors predicting response to treatment

Myositis-specific autoantibodies can play a role as predictors to therapy. Patients with anti-Jo-1 antibody against histidyl-tRNA synthase seem to respond inadequately to treatment and have a worse prognosis, possibly due to the fact that this antibody is related to ILD [43]. Additionally, patients with anti-SRP and anti-Mi-2 antibodies seem to be associated with better therapeutic response rates and long-term prognosis [41,60,61].

v) Impact of treatment in both malignancy and DM or clinical courses of malignancy in myositis

It is of high significance that some questions be answered, like how and whether cancer treatment in patients of DM may influence the status of myositis, and if malignancy recurrences associate with DM relapses and *vice versa*. DM-associated malignancy does not seem to affect myositis severity, degree of muscle strength impairment or its laboratory characteristics [27]. In a survey of cancer-associated myopathy (CAM) and patient prognosis, cancer surgical removal led to DM improvement in approximately 40% of them [37,62]. Evidence on better effects in DM course after tumor therapeutic management and DM deterioration is provided through case reports [63,64]. In addition, when cancer recurs, DM's inadequate response to treatment may increase the suspicion of an occult malignancy, especially at an advanced stage [3,27]. In terms of prognosis, almost 30% of DM patients remain severely disabled even after treatment, with the 5- and 10-year prognosis to come up to 95% and 84%, respectively [18,65].

Conclusions

Early DM recognition is critical, but can be quite complex due to diverse diseases and overlappings. The use of clinical features presented in this article can further enable physicians to more confidently differentiate DM and improve patient care.

Conflict of interests

The authors declare no confict of interests.

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