Case Reports

Two cases of dermatomyositis: so similar and yet so different

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Abstract

Dermatomyositis is a rare multisystemic autoimmune disease, the main clinical symptoms of which are muscle weakness and a characteristic rash. With the forms of treatment currently available, the 5-year survival rate is over 90%. However, there is a group of patients in which dermatomyositis takes the form of paraneoplastic syndrome and, in these cases, the response to treatment decreases and the prognosis is more reserved.

The authors present clinical cases of two 68-year-old men, with muscle weakness, dysphagia and characteristic rash, but with different treatment responses and clinical results, which reflected the influence of an associated neoplastic disease on the evolution of the dermatomyositis.

Key words: Dermatomyositis, inflammatory myopathies, neoplasia.

Introduction

Dermatomyositis (DM) is a rare pathology, which is more frequent among females, with a ratio of 2:1.[1,2] It presents bimodal distribution with two peaks of incidence: the first in infancy (juvenile DM) and the second between the 4th and 6th decades of life (adult DM).[1,3] The latter can also be divided into primary or idiopathic DM (the majority of cases), DM associated with neoplasia, and DM associated with diseases of the connective tissue (overlap syndromes).[3,4]

The etiopathogeny of DM is still not well-known, and lesions of the muscle fibers and the remaining organs have been attributed to individual genetic factors, viral infections and dysfunction of the immune system. It appears to start with endothelial deposits of the complement factor C5b-9.[1,3,4]

The most common typical cutaneous manifestations are Gottron nodules (purple plates or papules over the joint protuberances), heliotropic exanthema (purple erythema of the periorbital region, sometimes with edema of the eyelids), dermatitis in the areas exposed to light, telangiectasies, and periungal erythema. The cuticles may become irregular, thickened and distorted, and the palms of the hands and sides of the fingers may become rough, with dark, horizontal cracks, similar in appearance to the hands of a mechanic.[1,3,4]

Myositis is less evident at the time of diagnosis, and is generally associated with exanthema within two months.[3] It mainly affects the pelvic and scapular girdle muscles and the anterior neck flexors, in symmetrical form, evolving over weeks or months. The lower limbs are generally affected first, then the upper limbs, followed by the neck flexors, making it difficult for the patient to raise his/her head from the pillow. The involvement of the striated muscles of the hypopharynx and the upper third of the esophagus leads to dysphagia.[1,3]

Patients with DM may also present systemic signs and symptoms. The heart may be affected in any phase of the disease, and respiratory insufficiency may occur due to weakness of the respiratory muscles, interstitial pulmonary disease, methotrexate pneumonitis or aspiration pneumonia.[1,4]

Of the muscle enzymes, Creatine phosphokinase (CK) is the most sensitive and reliable indicator. Its blood serum levels are generally related to the activity of the disease, but may be normal in cases of active myositis.[1,3,4]

Although characteristic, electromyogram (EMG) alterations are not diagnostic, but enable to differentiate muscle weakness of neurological origin. Also, by

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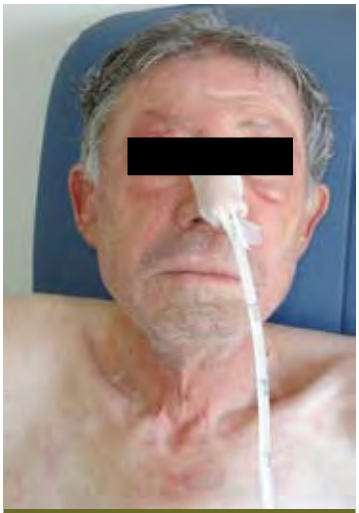
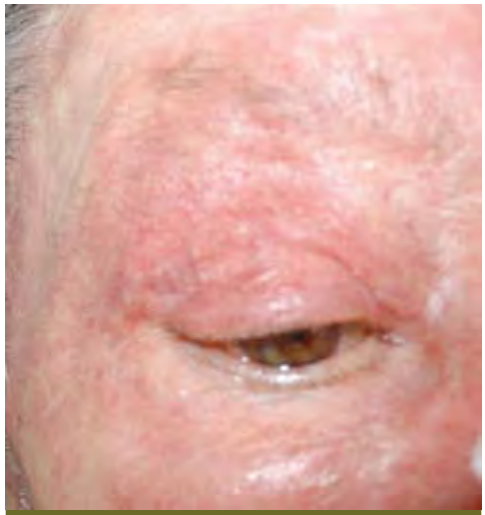


Edema and erythema of the face, erythema of the neck and upper region of the trunk in the form of a V (shawl sign).

FIG. 1



Heliotropic exanthema.

FIG. 2

indicating areas of active myositis, EMG can guide the biopsy. In DM, the inflammatory infiltrate is predominantly perifascicular lymphocytic, and endothelial lesions in the muscular microcirculation, ischemia, and perifascicular atrophy are detected. Even in the absence of inflammation, perifascicular atrophy confirms the diagnosis.[4]

The role of antibodies in DM has been the object of numerous studies, in which the physiopathological process has been involved in a continual, but non-definitive way. Antinuclear antibodies (ANA) are more frequent in DM associated with diseases of the connective tissue. The antibody anti-M2 (detected in around 15% of patients[1]) is associated with typical exanthema and a good therapeutic response. Of the anti-synthase antibodies, anti-Jo1 is highlighted, the most specific DM antibody, and the one which is associated with higher incidence of interstitial pulmonary disease, arthritis and Raynaud's phenomenon.

Clinical case 1

Male patient, aged 68 years, admitted to the Medical Service of the Hospital de Tomar in May 2005, with edema and non-pruriginous erythema of the face and neck, with about 1 month of evolution, and progressively worsening dysphagia in the last week. The patient had a history of gastric adenocarcinoma (T3N2M0), and underwent palliative subtotal gastrectomy in August 2004 and chemotherapy until December of the same year. He was not medicated at that time.

On objective examination, the patient was alert, cooperative and oriented, though thin, apyretic and eupneic; TA 175/96 mmHg; pulse 86 ppm rhythmic. Presented edema and erythema of the face, which was more pronounced in the periorbital region, notably on the upper eyelids, and erythema of the neck and upper region of the trunk in the form of a V (*Figs. 1 and 2*). Cardiopulmonary exam showed no alterations. Abdomen depressible and painless, without organomegalies or palpable masses. No peripheral edemas or palpable adenomegalies in the superficial ganglionar chains. In the neurological exam, dysphonia and dysphagia for solids and liquids were highlighted. The vomiting reflex was maintained and the uvula centered, without deviations, the movements of the velum and the tongue remaining symmetrical. In relation to the limbs, there was a marked decrease in proximal muscle strength. Sensitivity and osteotendinous reflexes showed no alterations. Observation by the ear, nose and throat specialist was requested: except for abundant sialorrhea, the specialist did not observe any lesions of the hypopharynx, larynx, or vocal chords.

Analytically, the patient presented normocytic and normochromic anemia (Hg 10.3 g/dL) and elevation of creatine phosphokinase (CK 2413 U/L with MB fraction 198 U/L), lactic dehydrogenases (LDH 1420 U/L) and glutamic-oxalo transaminase (GOT 124 U/L), the remaining values of the hemogram, routine biochemical evaluation and thyroid function being within the normal parameters. Antinuclear antibodies and anti Jo-1 were negative. CEA and CA 19.9 serum levels were doubled compared with the evaluations of the previous month.

CT scan of the neck, chest, abdomen and pelvis was performed, showing nodular lesion in segment VII of the liver, suggestive of secondary lesion and evidence of post-gastrectomy status. Upper digestive endoscopy did not identify any lesions suggestive of

TABLE I

Start of corticotherapy

Blood serum levels of	Date of admission	After 3 weeks	After 4 weeks	After 7 weeks
CK/CKMB (35-175 U/L)	1420 U/L	778/51 U/L	228 U/L	78 U/L
LDH (265-500 U/L)	2413 U/L	1183 U/L	900 U/L	502 U/L
TGO (15-41 U/L)	124 UL/L	62 U/L	47 U/L	20 U/L

neoplasia. CT and RMN CE revealed demyelinization of a vascular nature. Based on the hypothesis of dermatomyositis in the context of paraneoplastic syndrome, the patient was submitted to electromyography, which confirmed lesion of the muscle fiber. Muscle biopsy was carried out, which showed inflammatory infiltrate and perifascicular atrophy compatible with the diagnosis of dermatomyositis.

The patient began therapy with prednisolone (1mg/K/day – 60 mg/day), with a progressive reduction of CK, LDH and TGO values, normalizing in the seventh week of treatment *(Table I)*. This biochemical regression was accompanied by partial regression of the cutaneous lesions and the dysphonia, and an increase in proximal muscle strength of the limbs. Due to the persistence of the dysphagia, the patient remained dependant on a nasogastric probe. At the end of two months, corticotherapy was gradually reduced to a daily dose of 40 mg. Despite the biochemical stability, the patient's state worsened quickly and progressively, until he died.

Clinical Case 2

Male patient, aged 68 years, referred to the External Internal Medicine Consultancy of the Hospital de Tomar in January 2007, with erythema of the face and high CK in the analytical exams.

Patient reported non-pruriginous erythema of the face for around three months, and was therefore observed by a Dermatology clinic, initiating topical treatment with betamethasone. Due to failure of the treatment, the assistant doctor requested analyses which showed high levels of CK (1205 with fraction MB 45 U/L), LDH (821 U/L) and TGO (78 U/L), and the patient was referred to the Medical consultancy for further study. The patient also reported slight upper dysphagia, particularly for solids, muscle pain in the scapular region and thighs, and becoming fatigued easily with little effort, with difficulty climbing stairs, getting up from a seated position and raising the arms to shave and mainly to comb the hair.

The personal history included partial prostatectomy in 2004, due to benign hyperplasia of the prostate. Patient denied any subsequent therapy and was not medicated with other drugs, except for topical betamethasone.

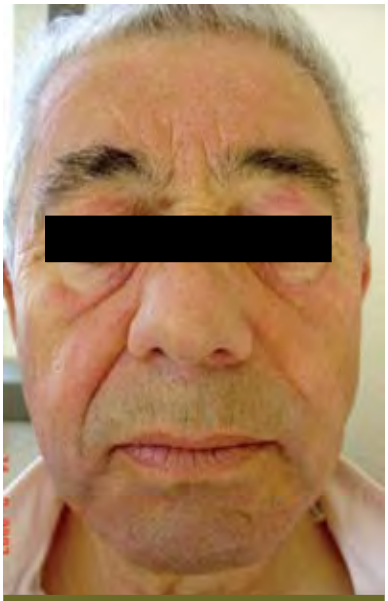
On objective examination, the patient was alert, cooperative and oriented, with good general and nutritional state. Apyretic and eupneic; TA 132/75 mmHg; pulse 72 ppm rhythmic.

Slightly scaled erythema of the periorbital region, particularly the upper eyelids, neck, and upper region of the trunk in the form of a V *(Fig. 3 and 4)*. Periungal erythematous lesions were seen, and irregular, thickened cuticles *(Fig.5)*. Cardiopulmonary and abdominal exam showed no alterations. No edemas or palpable adenomegalies. In the neurological exam, a slight decrease in proximal muscle strength of the upper and lower limbs was observed.

Of the complementary exams carried out, ANA, anti Jo-1 and anti-m2 negative antibodies are highlighted. Thyroid function was within the normal parameters. EMG showed signs of lesion of the muscle fiber in the proximal muscles of the limbs. Muscle biopsy was carried out, revealing atrophic muscle fibers with an increase in the number of nucleolar centralization, foci of inflammatory infiltrate, mainly in the perivascular region, necrosis and myophagocytosis *(Fig.6)*.

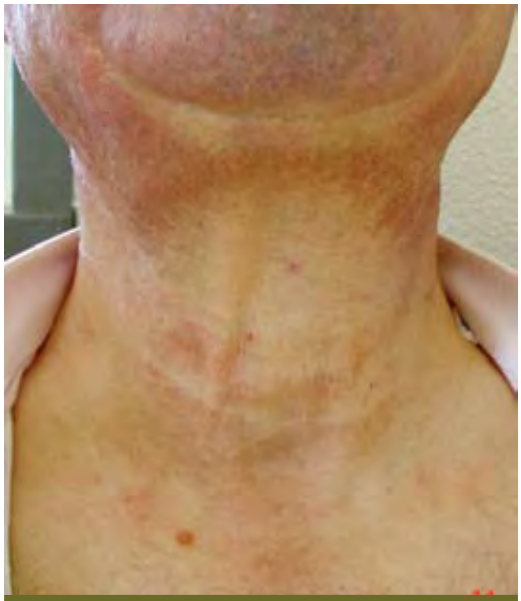
To study any coexistent neoplastic disease, upper digestive endoscopy, colonoscopy, Chest and pelvic CT, and prostate echography were requested, which did not show any alterations. PSA level was within the normal parameters.

Prednisolone 80 mg/day (1 mg/K/day) was initiated, with analytical regression at 3 weeks *(Table II)*. There was marked clinical improvement, with a decrease in pain complaints and recovery of proxi-



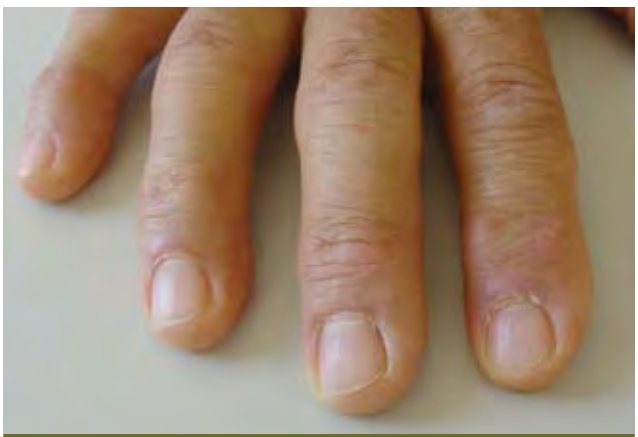
Erythema of the face, known to be predominantly in the periorbital region, slightly scaled.

FIG. 3



Erythema of the neck and upper region of the trunk (shawl sign).

FIG. 4



Thickened and irregular cuticles and periungal erythema.

FIG. 5

mal muscle strength, however some dysphagia and the erythema remained. Therapy was initiated with hydroxychloroquine and topical betamethasone, with improvement of the cutaneous lesions. At the end of eight weeks, reduction of the prednisolone dose was initiated, and the patient was followed-up at an external clinic, without worsening of the symptoms.

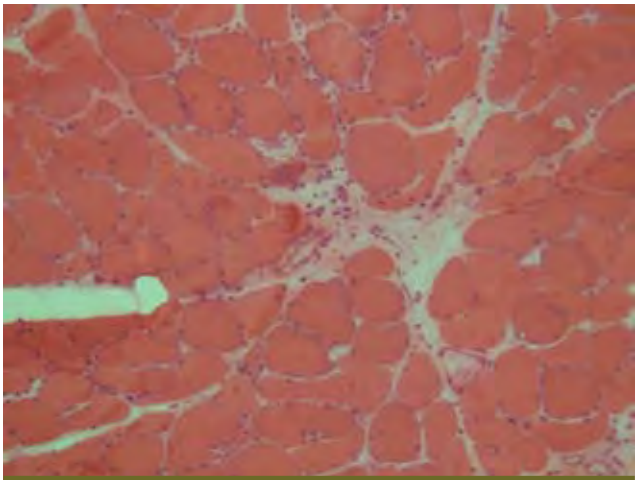
Discussion

The association between inflammatory myopathies and neoplasias was described, for the first time, in 1916, in a patent with gastric neoplasia. Since then, various works have reinforced this connection. A study published in 1992,[5] involving 392 patients, showed an incidence of neoplasia of 15% (and cause of death in 40%) in patients with DM and 9% in patients with PM. This difference was also evident in a study published in 2001[6] involving 537 patients, in which neoplasia was diagnosed in 42% of patients with DM compared with 18% in patients with PM, and 27% in DM associated with diseases of the connective tissue. It was also demonstrated that this association was more frequent in individuals over 65 years of age.[7]

The reason for the higher incidence of neoplasias in these patients is not known. One hypothesis that has been suggested is that both DM and neoplasias may be unleashed by a toxic or infectious agent, in genetically predisposed individuals. Alternatively, neoplasias may be induced by the immunosuppression of the DM treatment. Another hypothesis supports the existence of a crossed reaction between antigens of the tumor and of the muscle tissue.[8]

DM can be associated with any type of neoplasia, the most frequent being carcinomas of the lung, ovary, breast, cervix of the uterus, colon, stomach, bladder, melanoma and non-Hodgkin's lymphoma.[3,4,9]

In the first clinical case, DM was diagnosed 1 year after the gastric tumor, which is in accordance with the literature, which reports that in the majority of cases, the diagnoses of DM and neoplasia are made within less than one year.[10] Often, however, the neoplasia is diagnosed after this period has elapsed. According to the same author, the relative risk for neoplasias is around 6 times higher than that of the general population in the first year after diagnosis of DM, but decreases to 2-3 times in the subsequent year, gradually continuing to decrease, such that long-term



Enlarged 10 times. Hematoxylin-eosin coloration – atrophic muscle fibers with increase in the number of nucleolar centralizations, foci of inflammatory infiltrate mainly with perivascular location, necrosis and myophagocytosis.

FIG. 6

follow-up is no longer required.

DM may evolve independently of neoplasias or, as occurred here, it may follow its course (paraneoplastic syndrome) going into remission when the neoplasias is cured, and emerging/recurring when the tumor or its metastization return.[3] However, the investigation of a hidden tumor should not be done through a battery of costly, invasive and random exams, but should be guided by an anamnesis and an exhaustive objective exam, followed by radiographic and laboratory evaluation of the chest with complete hemogram and platelets, sedimentation speed, blood biochemistry and Urine II. CA-125 dosage and gynecological echography should be included in the study, in females, and evaluation of the PSA in males over 50 years of age.[3] CT of the chest, abdomen and pelvis has also been suggested by some authors,[9,11] particularly in patients at higher risk (aged over 65 years, and those with significant weight loss or a history of neoplasia) for whom an endoscopic digestive study by colonoscopy is also recommended.[7] This evaluation should be repeated annually in the first 2 to 3 years after diagnosis (5 years for tumor of the ovary[12]) and after that, according to the clinic, or as stated above, whenever there is recurrence of the DM.

The treatment should be initiated quickly, with the aim of improving muscle strength and not only reducing/normalizing CK levels, since a drop in these levels is not always accompanied by clinical improvement, the most faithful indicator of the therapeutic response.[3,4]

Corticotherapy in high doses has been used empirically as the treatment of first choice.[1,3] Although it has not been demonstrated to increase survival, the general consensus is that it improves muscle strength and preserves muscle function.[13] It is recommended that prednisolone be initiated at a dose of 1.5 mg/Kg/day, according to the severity of the disease (methylprednisolone pulses of 1g ev 3 days has been used at the start of treatment in patients without oral route or with more severe clinical states).[1,3] This dose should be maintained - unless intolerable side effects occur - until there is clinical improvement and normalization of the CK, which occurs, on average, within 4 to 8 weeks. Once a response is obtained, the prednisolone dose should be slowly reduced, to a minimum effective dose (on average 5mg/week[1]).

The treatment is very successful in the majority of cases (50-90% according to the series), particularly when initiated early, and the response is substantially lower when the treatment is initiated more than 4 months after the onset of the muscle weakness. As the clinical case presented here appears to reflect, in paraneoplastic DM, the probability of therapeutic failure is greater, since after an initial response, progressive muscle weakness tends to occur.[3]

The failure of corticotherapy should lead to the hypothesis of an alternative diagnosis. If a patient responds initially to corticotherapy but suddenly stops improving or his/her clinical state worsens, two situations should be considered: 1) the existence of a neoplasia which has still not been diagnosed 2) myopathy which

TABLE II

Start of corticotherapy

Blood serum levels of	Date of admission	After 2 weeks	After 3 weeks
CK/CKMB (35-175 U/L)	1205/45 U/L	927/116 U/L	135 U/L
LDH (265-500 U/L)	821 U/L	760 U/L	538 U/L
TGO (15-41 U/L)	78 UL/L	65 U/L	30 U/L

is toxic to corticoids. The absence of spontaneous fibrillation in the EMG or selective atrophy of the type II muscle fibers without inflammation, associated with muscular biopsy, are two data which support this hypothesis. Unfortunately, in practice, these alterations coexist with those of DM itself, making it difficult to interpret the exams, therefore the clinical response to reduction of corticotherapy may be a good indicator to follow in the practical approach to this dilemma.[3]

If there is no response at the end of 3 months, the DM should be considered corticoresistent, and the association of immunosuppressors is indicated.[3,4]

In reality, around 75% of patients will require additional treatment at some point in their disease.[4] Immunosuppressors may also be associated as corticoid sparing drugs, or for more severe and progressive cases, with marked muscle weakness and respiratory insufficiency.[1,3,4]

Of the most commonly used drugs, azatioprin has a slow clinical response (2 to 3 months after it is initiated), therefore it is associated with corticoids in an attempt to suspend or maintain the minimum dose possible.[1,4] Some patients who are resistant to corticoids and azatioprin respond to methotrexate, whose usual initial dose of 7.5 mg/week can be gradually increased to 25 mg/week.[1,4] As these are drugs with major side effects, patients should be monitored on a regular basis. The treatment is maintained for around 2 years before attempting to stop all the medication, which should be done gradually.[1] The use of endovenous immunoglobulin, although costly, has proven effective in patients who do not respond to other treatments. The maximum response is generally seen after 3 to 4 administrations, and long-term treatment is necessary, to maintain the results.[3,4] Cyclophosphamide, cyclosporin, plasmapheresis and body irradiation have also been used, but with less consistent results.[1,4] More recent therapeutic agents such as tacrolimus, mycrophenate mofetil, alfa tumor necrosis inhibitors or Rituximab have been the target of more recent investigations, with promising results.[4,14]

Cutaneous lesions may not respond to treatment as well as myositis. Topical corticoids and hydroxychloroquine have been used, with good response, while chloroquine phosphate and quinacrine are alternative drugs. Protection against exposure to the sun and the use of sunscreen are of vital importance.[3] Rest is advisable during the active phase, and gentle physiotherapy is indicated for bed-ridden patients, to prevent contractions, and exercise should be maintained according to the patient's tolerance, for those with less severe conditions and during the recovery phase. A high-calorie, low-glucose, high-protein, low-salt diet should be given, but the dysphagia may necessitate feeding via a nasogastric probe.[1]

The clinical evolution of DM is highly variable, little studied and difficult to predict. In a study published recently, which evaluated the evolution of 165 patients over a 5-year period, 60% of the patients presented a chronic course, 20% presented polycyclic disease and 20% presented monophasic disease.[15]

Besides the coexistence of neoplasias, other factors have been associated with poor prognosis in the evolution of DM: major muscle weakness at the time of diagnosis, quick development of the clinical condition, the existence of dysphagia, cardiac or pulmonary involvement, age, and delayed initiation or poor response to the treatment.[1,3,4] On the other hand, the association of diseases of the connection tissue may be considered a factor of good prognosis, as it is associated with a lower probability of neoplasia, and may often respond well to low doses of corticoids.[3]

Conclusion

The clinical cases presented here are an example of how DM, a disease with such characteristic clinical and laboratory signs and symptoms, may have such different meanings. Two patients of the same sex and age, with similar clinical conditions, varying in intensity and time of evolution (3 months in the first, and 1 month in the second), differing mainly in relation to personal history, and previous neoplasia without curative treatment in the first case. Widely recognized as a factor of poor prognosis, the tumor advanced in his natural history, accompanying the DM in the form of paraneoplastic syndrome, with partial initial response to treatment. However, the worsening of the patient's general state made interpretation and therapeutic indication of the case difficult (cachexia versus myositis), leading to a fatal inevitable outcome. In the second case, although diagnosed at the end of three months after the onset of symptoms, the clinical state was less exuberant and the response to treatment more complete. The initial study dismisses, for now, the coexistence of neoplasia, and the best possible evolution is expected, while continuing with the investigation. ■

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