Dermatomyositis – treatment challenges?

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Abstract

The major inflammatory myopathies – dermatomyositis, polymyositis and inclusion body myositis – are uncommon and can be difficult to distinguish from many conditions emulating them clinically. They have a high morbidity and are not infrequently the first sign of an associated malignancy and they may be a part of another connective tissue disease.

The treatment of the idiopathic inflammatory myopathies is challenging for a number of reasons – patient heterogeneity, limited clinical trial data and suboptimal assessment tools to quantify the disease activity and damage and reliably distinguish between them. Despite these limitations and challenges, and after confirming the diagnosis, determining the clinical and serologic subgroup of the patient, assessing extra muscular manifestations and defining the relative contribution of disease activity and damage to the patient's condition, a therapeutic plan should be developed and followed.

Although corticosteroids remain the mainstay of an initial treatment plan, combination immunosuppressive regimens and other novel disease-modifying immunologic agents are new additions to the therapeutic arsenal of inflammatory myopathy. Rehabilitative measures and physical therapy interventions are critical elements to include at every stage in the treatment plan.

The authors present two cases of dermatomyositis, illustrate some of the complexities in the presentation and natural history of these disease and the benefits of intensive therapy.

Key words: dermatomyositis, prednisolone, azathioprine, immunoglobulin, methotrexate, cyclophosphamide.

Introduction

Idiopathic inflammatory myopathies are a group of heterogenous systemic rheumatic diseases including Polymyositis (PM), Dermatomyositis (DM) and Inclusion body myositis (MCI) and are featured by a proximal symmetric muscle weakness secondary to a chronic inflammation of the muscular tissue, differentiating each other due to clinical and histopathologic features.[1]

Clinically, the diagnosis criteria proposed in 1975 by Bohan and Peter, combining clinical, laboratorial and histopathological features, remain as acceptable and widely used.[2,3,4] The first four criteria relate with the muscle illness – proximal muscle weakness, symmetric and progressive, increase on the serum concentration of muscles enzymes, abnormal electromyography and compatible muscle biopsy – and the latter corresponding to the remaining inflammatory myopathies. In fact, due to the semiology and therapeutic similarity with polymyositis, DM is usually described with this one, being different only in the typical cutaneous involvment.[1,5,6,7]

The definite diagnosis of inflammatory myopathy requires a muscle biopsy, enabling also to exclude many of the entities which may emulate it. Electromyography and imagiology study, particularly, magnetic resonance imagiology are additional useful diagnosis tools. This, whilst defining active muscle inflammation areas, reduces the rate of false negative associated to the biopsy (estimated in around 10-25%).

Inflammatory myopathy treatment, in spite of the recent advance in immunosuppressant schemes remains a true challenge, even for the most experienced physician. The scarcity of prospective clinical studies in this area, comparing different treatment approaches, emerges from its rarity, together with its heterogenous and sometimes systemic manifestations, leading to unique presentations, of variable severity with different therapeutic implications.

In spite of limitations and challenges, a rational

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and systematic approach is essential. Once the diagnosis of inflammatory myopathy is established, it is compulsory to identify its subtype, as for instances, the MCI patient not only has a unique clinical presentation, but responds to therapy in a different way that the one verified in patients with PM, DM and *overlapping syndromes*. Besides, a number of serial auto-antibodies may anticipate potential systemic complications, different responses to treatment and different clinical courses, therefore its characterization may have a therapy and prognosis usefulness[8]. Due to the systemic potential of inflammatory myopathies it is crucial to evaluate each patient on extra-muscular compromise, in order to establish an optimal treatment. The patient total evaluation may, depending on signs and symptoms, include an echocardiography, respiratory function tests, high resolution pulmonary CAT scan, as well as gastroesophageal motility studies.

Case 1

42 years old female without relevant history, admitted due to a progressive asthenia condition, adynamia, bilateral lumbar pain with paroxystic radiation to the dorsal and cervical region, and proximal symmetric muscle weakness involving the scapular and pelvic girdle with significant functional impact, progressing for 3 months. She mentioned in the last weeks, a scaling pruriginous erythema in the palm of her hands, arthralgias in the elbows and knees, without associated inflammatory signs, and progressive dysphagia for solid food, with oropharynx predominance.

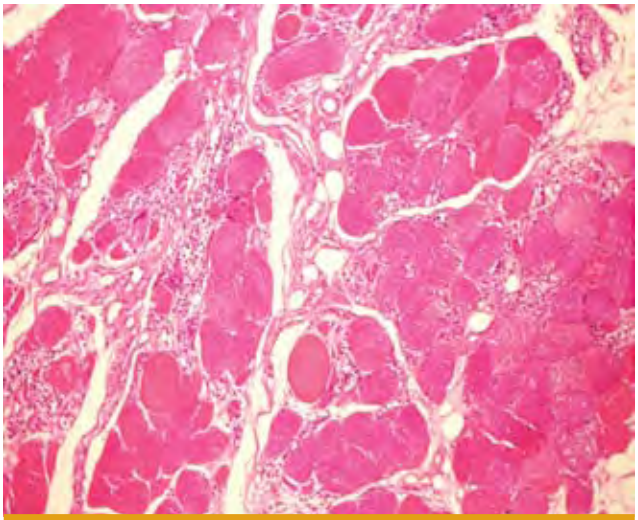
On admission, she presented a general facial erythema with periorbital edema, scaling hyperkeratosis lesions in the palm of her hands, with cuticular dystrophy associated and periungal telangiectasies, limb proximal muscle weakness (grade 3/5) and head-drop towards the left. Analytically, she presented normal hemogram and leukogram, C-protein reactive 11.37 mg/dL, sedimentation rate 24mm/h, creatinine kinase of 5179 U/L, lactic dehydrogenase of 1820 U/L, aspartate aminotransferase of 176 U/L, with normal thyroid function and normal gasometry. The immune study has only revealed positive antinuclear antibodies 1:160 with nucleolar pattern and positive anti-histone anti-top-I/SC1-70 (1+), with negative results to the remaining specific auto-antibodies or associated with myositis (JO-1, SRP, Mi 2, Ku, snRNP). Electromyography has revealed suggestive signs of moderate to serious myopathy, with presence of spontaneous denervation potential at rest. The muscular biopsy of the right deltoid muscle has shown skeletal muscle tissue with degenerative alterations in the muscle fibers and with a moderate polymorphic inflammatory infiltrate, perivascular, in the perymisium region, compatible with a clinical hypothesis of dermatomyositis *(Fig 1)*.

A double treatment was started with prednisolone 1.5mg/kg/day associated to azathioprine 2mg/kg/day, together with an assisted program of physical rehabilitation.

With negative tumoral markers, the patient underwent upper gastrointestinal endoscopy, total colonoscopy, abdominal and pelvic ultrasound, mammography and cervico-vaginal cytology that beyond normal have excluded any underlying malignancy.

Due to sinusal bradycardia during the first five days of admission she was submitted to Holter, showing a sinusal rhythm during all the record, with rare supraventricular extrasystole and very rare isolated ventricular extrasystole, with bradycardic activity for a great part of the recording time and the echocardiography was normal. The thorax high resolution CAT scan has shown areas of densification discreet in the pulmonary parenchyma with a draft pattern of unpolished glass, relatively scattered, suggesting alveolar interstitial pathology, compatible with breathing functional tests, showing a moderate restrictive ventilatory syndrome and reducing the single breath alveolar-capillary transfer of carbon monoxide.

It was started, with the baseline therapy, on the 5th day of admission, monthly pulses of methylprednisolone, 1g/day for three days and immunoglobulin, 2g on the 4th day, with a gradual improvement of the muscle strength and dysphagia, a complete resolution of bradycardic activity and gradual analytical normalization. Cutaneous lesions have been fading away. She was discharged, keeping only a muscle weakness grade 4/5. She completed eight monthly cycles of methylprednisolone and immunoglobulin, an ending coinciding with the azathioprine gradual reduction and introduction of methotrexate 7.5mg/week. Since then, with a gradual improvement of muscular strength up to normal, time in which it was started a gradual reduction of the baseline prednisolone in 25% of the dosage every three months, keeping a total illness remission.



Muscle biopsy showing skeletal tissue with degenerative alterations foci in muscular fibers and with a moderate polymorphic inflammatory infiltrate, perivascular, in the perymisium. (hematoxylin-eosin staining)

FIG. 1

Case 2

16 years old adolescent, female, without relevant pathologies or family history, referred to hospital due to a progressive condition of asthenia, anorexia, proximal predominant myalgias, attaining the scapular and pelvic girdle and lumbar and cervical regions, periorbital edema and unspecific polyarthralgias, mainly during the day, evolving for two weeks. In the last couple of days, she mentioned mainly proximal dysphagia for solid food.

At arrival, her condition was compatible with symmetric proximal myopathy, with myalgia and pain to palpation of muscle groups in both arms and difficulty getting up against gravity by upper and lower limbs, with a muscle strength grade 4/5 and moderate edema at upper limb level and periorbital. Analytically with normal hemogram and leukogram, C-protein reactive 15.46 mg/dL, sedimentation rate 32mm/h, creatinine kinase de 10901 U/L, lactic dehydrogenase 1820 U/L, aspartate aminotransferase 1083 U/L, with normal thyroid and kidney functions and normal gasometry. The immunology study has shown positive antinuclear antibodies 1:80 with nucleolar pattern and positive antibodies anti-SSA/Ro52 and anti-Topo-I/SCl-70 (1+), with negative anti-dsDNA. Negative specific or associated auto-antibodies associated to myositis (JO-1, SRP, Mi 2, Ku, snRNP). Negative infectious serology.

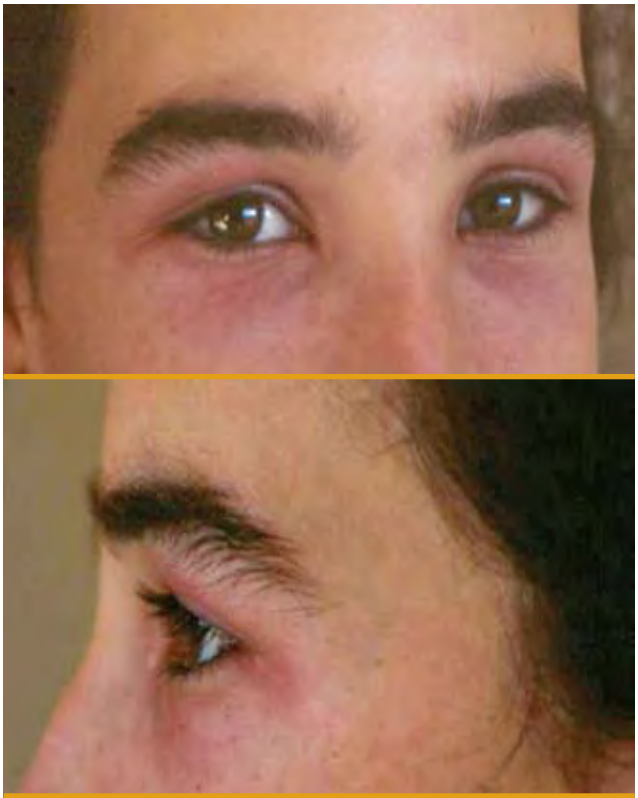
On the second admission day she started a characteristic heliotrope rash *(Fig. 2)* and palmar erythema with ungual telangiectasy and cuticular hypertrophy *(Fig. 3)*. The right deltoid muscle biopsy has revealed multiple rhabdomyolysis foci associated to an inflammatory infiltrate predominantly perivascular and lymphocytary, but also interstitial, focally with histiocyte presence around necrotic muscle fibres, concluding as myositis framed as a dermatomyositis condition *(Fig. 4)*. Electromyography has shown a normal peripheral nervous conduction, with a trace with myopathy features and rest potential consistent with severe inflammatory myopathy.

It was started, on the 2nd admission day, oral prednisolone 1mg/kg/day, with a gradual improvement of cytolytic markers never reaching, however, the normality and without an evident clinical improvement. On the 15th admission day, by sustainable total dysphagia, needing feeding by nasogastric intubation, fulminant deterioration of muscular weakness (tetraparesis grade 2/5) and analytical deterioration of muscle cytolysis markers, replaced the therapy to prednisolone 2mg/kg/day, through a venous route, associated to azathioprine 2mg/kg/day and physical rehabilitation treatment.

The upper gastrointestinal endoscopy has only revealed hyperemia of the antrum mucosa, with a negative biopsy for neoplasm and *H. pylori*. The esophagic manometry has shown incapacity to swallow properly with transfer dysphagia involving the proximal pharynx muscles, and it is not seen, at esophagic level, normal characteristics peristaltic waves. The echocardiography was normal and the thorax-abdomen-pelvis CAT scan, a part of excluding a neoplastic pathology associated, revealed at the level of the pulmonary parenchyma, mainly on the left, areas of higher density in an "unpolished glass" with acini type micronodules suggesting interstitial pneumonitis. Breathing function tests with a mixed ventilatory pattern and a reduced diffusion ability without an associated respiratory failure.

Without any clinical improvement, it was proposed fortnightly cycles of immunoglobulin 2g/kg, fortnightly pulses of methylprednisolone 30mg/kg, in three consecutive days and cyclophosphamide 1g/m2, weekly, in association with baseline therapy.

On the second treatment month, she presented a clinical and laboratorial improvement, with nor-



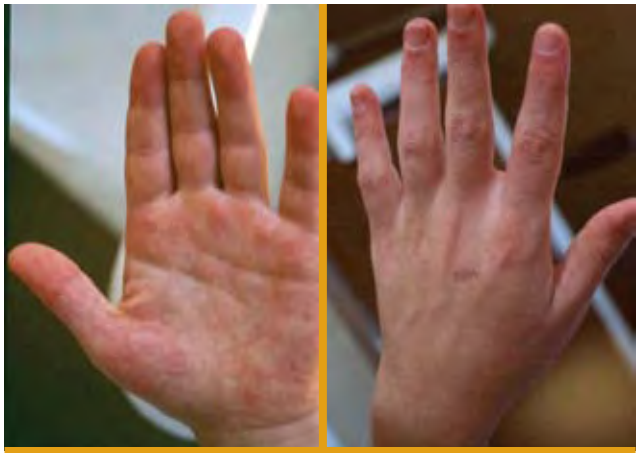
Heliotrope Rash .

FIG. 2

malization on muscular cytolysis markers without muscular cytolysis, without dysphagia and muscle strength grade 3/5. She was discharged home at the end of the third month, keeping the follow up as an outpatient and therapy in day hospital regime. The cyclophosphamide weekly cycles were gradually withdrawn, followed by the fortnightly cycles of methylprednisolone and immunoglobulin, time in which she started methotrexate 7.5mg/week in one take. Since then, with a progressive, asymptomatic improvement and with a muscular strength grade 5/5. It was then initiated, a progressive weaning off of baseline corticotherapy and azathioprine, being at present under remission treatment with methotrexate 7.5mg/week and prednisolone 10mg/day.

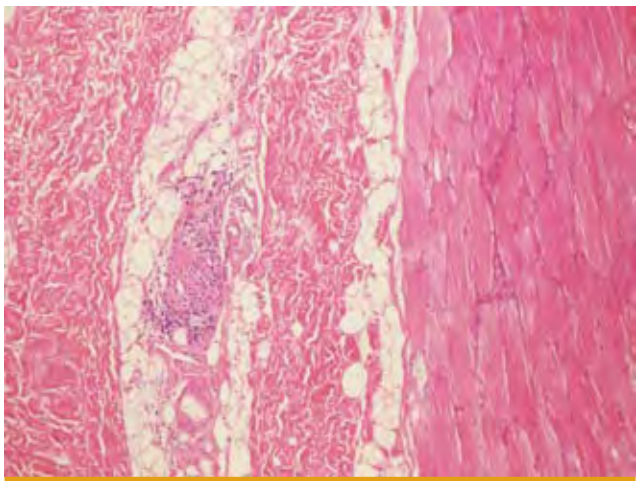
Discussion

Although it can occur in any age group, DM presents a bimodal distribution with incidence peaks in children from 5 to 15 years old and adults between 40 and 60 years of age, with a slight female predominance.[9]



Palmar erythema with ungual telangiectasy and cuticular hypertrophy.

FIG. 3



Muscle biopsy revealing multiple rhabdomyolysis foci associated with inflammatory infiltrate predominantly perivascular lymphocytary, but also interstitial, focally with histiocytes present around necrotic muscle fibres. (Hematoxylin-eosin staining).

FIG. 4

Heliotrope rash and Gottron´s papules are characteristic cutaneous lesions probably DM pathognomonic. The first is a periorbital reddish-purple (violaceous) rash, with or without associated edema, symmetrical and can vary from discreet to exuberant. [5,6] Gottron´s papules, or violaceous plaques, scaling to psoriatic, involving the joints extensor surfaces, mainly the metacarpophalangeal and interphalangeal, occur in 1/3 of patients, and can be taken by erythematous lupus

lesion, or sometimes, as psoriasis. Other cutaneous alterations, although frequent in DM, are not pathognomonic, namely malar erythema, poikiloderma in areas exposed to light and cuticular and periungal alterations (cuticular dystrophy, punctiform hemorrhage infarcts, periungal telangiectasies). A cutaneous calcinosis, occurring in 30-70% of juvenile dermatomyositis cases and in only 10% cases in adulthood, it is more frequent at wrists joints levels, elbows and knees and in areas subject to trauma, being associated to an increased disease activity with increased morbidity and mortality. The cutaneous involvement may precede the myopathy development and may persist even after the disease control and quiescence.[6] A small group of patients presents only a small cutaneous component of the disease, without ever evolving to myopathy being classified as presenting amyopathic dermatomyositis.[10,11] However, in such cases, the muscular biopsy, if performed, reveals a subclinical muscular involvement, with typical perivascular and perymisium inflammation.

Clinical and laboratorial changes of muscular involvement are primary characteristic of classic DM. Myopathy compromises primarily the proximal muscles, usually is symmetric progressing slowly for weeks and months. The initial symptoms include myalgias, fatigue, muscular weakness. Pain to palpation of muscular groups is variable.

DM is a systemic disease.[6] Arthralgias and arthritis, mainly of small joints as hands, elbows and knees, occur in around a quarter of patients, usually followed by morning stiffness. Esophagic disease is present in around 10-15% of cases, causing proximal dysphagia, secondary to striated muscle compromise, and depending on the disease seriousness and a rapidly progressive course, and/or distal dysphagia, due to the smooth muscle involvement, which is common in patients with overlapping syndrome with scleroderma. Dysphagia on its own is a sign of bad prognosis as it is related with concomitant pulmonary involvement. Pulmonary disease occurs in about 15-30% of patients, with interstitial pneumonitis being the secondary process the most frequent. When it occurs, it is a bad prognosis factor and patients with anti-synthetase auto-antibodies have a special predisposition for it. Respiratory functional tests with diffusion ability and the typical findings in high resolution CAT scan are highly sensitive to its detection.[6] Symptomatic cardiac disorder seldom happens, but when it does it is also a bad prognosis factor. A number of alterations have been described, namely conduction defects, arrhythmias, pericarditis, myocarditis, dilated cardiomyopathy and valve disease.

Once the clinical suspicion arises, the laboratorial study should reveal an increase in the serial concentration of muscular enzymes (creatinine kinase, aldolase, lactic dehydrogenase and aspartate aminotransferase). The immunologic study is usually positive for antinuclear antibodies. Several autoantibodies are strongly associated with certain subclinical types.[12] Anti – Jo-1 antibodies are associated with pulmonary involvement [13] (interstitial pulmonary disease). The so called anti-synthetase syndrome (anti-Jo-1) is typically featured by fever, Raynaud's phenomenon, arthritis, interstitial lung disease and 'mechanic´s hands'. Anti-Mi-2 patients usually present rash involving trunk and back, with more favorable responses to treatment, being highly specific to dermatomyositis. Patients with anti-SRP present a more aggressive disease of sudden onset. Other autoantibodies as anti-PM-Scl and anti-Ku, are associated with overlapping syndromes as scleroderma.

Electromyography reveals spontaneous activity increased with fibrillation, complex repeated discharges and peak positive waves. The voluntary motor units consist of polyphonic low amplitude units.[5] These changes, although not pathognomonic confirm the existence of active myopathy.

Muscular biopsy confirms the diagnosis. Inflammation is predominantly perivascular, perymisium and interfascicular septum. Muscle fibres undergo phagocytosis and necrosis, usually in groups (microinfarctions), involving a portion of a muscle fasciculum or its periphery, resulting in perifascicular atrophy, which is a disease.[14]

In spite of all inflammatory myopathies being associated to an increase neoplastic risk, especially in older patients, this association is clearer in DM.[11] The association dermatomyositis to neoplasm (breast, ovary, womb, lung, stomach and non-Hodgkin lymphoma, more frequently) occurs in around 20-25% of cases and can precede or follow the diagnosis or emerge at a later stage.[15] An annual screening with a complete physical exam, pelvic ultrasound, cervicovaginal cytology, mammography and conventional thorax X ray is usually enough and should occur at least in the first three years of the disease.

After confirming the diagnosis, determining the

clinical and serological subtype, evaluating the extra-muscle manifestations and defining the disease activity (*versus* already established and irreversible lesions), must be established a multidisciplinary therapy plan, in which must be included decisions on the method of monitoring the disease activity. Although muscular weakness is a critical indicator of the disease activity, it is hard to quantify. The manual test for muscular strength, using the Medical Research Council score 0-5, is a rough approach not very sensitive, particularly to detect small, albeit important, degrees of muscular weakness. More objective measurements, as an isokinetic dynamometer, are easier to reproduce but also more expensive and less available. However the isolated muscular function does not discriminate between active and chronic disease already with established and irreversible lesions, being needed a combination with the analytical study. Sedimentation rate and other acute stage reagents are only increased in a minority of patients, therefore they are not useful to evaluate the disease activity. Creatinine kinase serum activity (or of other muscular enzymes) may be useful to determine the disease activity, but the relationship is not straightforward, with improvement in the functional capacity seeming to be the most important indicator of therapeutic response.[8,16,17]

Physical treatment timing and aggressiveness and rehabilitation interventions have been a discussion issue over the years due to the risk of inducing flares in the disease.[1] However, recent studies have shown that exercise, beneficial to preserve and improve the muscular functional capacity, is safe without worsening the muscular inflammation, measured whether by the muscular enzymes serum levels or by muscular biopsy and magnetic resonance.[18,19] The current approach to non-pharmacological intervention must be systematized to each disease stage, combining progressively passive exercise to assisted programs helped by isokinetic and isometric exercises, and culminating in an aerobic conditioning.

The corticosteroids remain the basis of the inflammatory myopathies initial treatment, with dose depending on the disease severity and underlying risk factors for the inherent toxicity. A possible approach it is to start with an oral dosage equivalent to 1mg/kg/day in two daily takes.[1] Some authors advocate the use of initial pulses of methylprednisolone 3 days at 1g/day trying to shorten the disease course and inducing clinical remission. After bringing muscular enzymes to normal (usually after 1-2 months) and clinical inactivity, the dosage is consolidated in one single daily take and gradually reduced in 20-25% every 3-4 weeks, until reaching a daily dosage of 5-10mg, kept until at least one year of treatment. This represents a regime for the ideal patient, without aggravating factors, responding to corticoid treatment and does not show significant side effect to prolonged corticotherapy.

However, around 25-30% of patients do not respond to systemic corticoids, without response or multiple recurrences, and 25-50% develop important side effects related with corticoids.[1,6] Therefore, the early treatment with immunosuppressant agents, as methotrexate, azathioprine, cyclophosphamide, mycophenolate mofetil, chlorambucil or cyclosporine, may be effective to keep remission. In fact, immunosuppressants are effective agents as corticoids savers, in reoccurrence after repeated attempts of weaning off, in cases of progressive rapidly diseases compromising vital organs or in those patients simply refractory to corticotherapy.

In spite of the relative scarcity of studies, the immunosuppressant selection is no longer largely experimental and depending on the physician personal experience. Therapy with methotrexate and azathioprine is now considered a first choice, with clear advantage over other options. In a less conclusive fashion, before the published studies, other options are the cyclophosphamide, and in a subsequent level, cyclosporine and mycophenolate mofetil while waiting for Rituximab results.

Azathioprine (2.5-3.0 mg/kg, oral) has a significant corticoid saving effect, with a favorable functional clinic effect, when compared to a therapy with corticoid alone,[20] but with a latency time of around 3-4 months Methotrexate (7.5-10mg/week with 2.5 increments until a target dose of 25mg/week, oral), with a fastest action, it is considered a first line adjuvant therapy. A combination of oral methotrexate with azathioprine has an additional benefit to treat a condition resilient to corticotherapy.[21] A study has demonstrated that patients with anti-Jo-a antibodies present a clinical response more favorable to methotrexate, when compared to the one verified with azathioprine.[22]

Cyclosporine (100-150mg, 2 times a day, orally) has been described as having proven benefits in the treatment of juvenile and adult dermatomyositis. Mycophenolate mofetil (2g/day) has emerged as a

promising and well tolerated option, being effective not only to control the active disease, as potentially, being able to induced prolonged remission, and can avoid the need for corticoids in high dosages and long term treatments. At present, it may be an alternative to conventional immunosuppressant agents or the first line in some patients with severe disease.[23] Cyclophosphamide (0.5-1g/m2, endovenous) has shown a mixed result and seems to benefit the interstitial lung disease with a clinical major benefit in juvenile dermatomyositis (and possibly the adult) severe or refractory.[24]

In patients with severe myositis and serious extra-muscle manifestations (as interstitial lung disease or myocarditis), it is recommended to start a treatment combined with prednisolone and methotrexate or azathioprine,[25] due to a more likely possible remission. Other possibility is to institute intravenous pulses of methylprednisolone for a quicker disease control. Some studies have shown a benefit in the use of high dosages in these cases.[8,20] Intravenous immunoglobulin (1-2g/kg) has shown itself promising, being effective both in clinical improvement, which can be dramatic, even after the first session, as solving the underlying immunopathology, as demonstrated in repeated muscle biopsies.[1,26] However, its effects are short lasted, in need of repeat every 6-8 weeks. Isolated is not enough to suppress the disease activity,[8,27] therefore it is always necessary an underlying basis therapy.

More specific forms of treatment, targeting several pro-inflammatory cytokines (for example, TNF-α and IL-1ñ) and in B and T cells and its receptors, have shown to be promising in the treatment of refractory and resilient cases to the classic approaches.[28] Preliminary studies report a significant success rate with Infliximab and Etanercept.

Both cases presented by the authors illustrate the complexity and challenges while approaching dermatomyositis patients. Initial manifestations, clinical and laboratorial are unspecific, with variable severity grades that, in many cases justify aggressive treatments from the start, combining several immunosuppressant classes, with weaning off and maintenance schemes, tailored for each case. ■

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