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Mãos de Mecânico e Toxidermia à Hidroxicloroquina: Ferramentas Diagnósticas Preciosas

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RESUMO – O diagnóstico clínico de dermatomiosite é muitas vezes difícil e desafiante. A presença de uma história clínica clássica, aliada a um exame físico completo e ao uso dos anticorpos específicos para miosite recentemente descritos, pode levar ao diagnóstico mais precoce desta entidade. Desta forma e com o início atempado da terapêutica, minimiza-se o risco de progressão da doença.

Apresentamos o caso de uma doente com mãos-de-mecânico e uma história prévia de toxidermia à hidroxicloroquina. Embora estes achados não sejam patognomónicos de dermatomiosite, quando associados a uma história clínica e exame físico típicos, são ferramentas diagnósticas úteis.

PALAVRAS-CHAVE – Anticorpos; Dermatoses da Mão; Dermatomiosite; Enzimas Ativadoras de Ubiquitina; Erupção por Medicamentos; Hidroxicloroquina/efeitos adversos.

Mechanic's Hands and Drug Eruption to Hydroxychloroquine: Precious Diagnostic Tools

ABSTRACT – The clinical diagnosis of dermatomyositis can be difficult and challenging. In the right clinical setting and with the use of the recently described myositis specific antibodies, an earlier diagnosis can be made and therapeutic approaches promptly started, minimizing the risk of disease progression.

We herein present a case of a patient with mechanic's hands and a previously documented drug eruption to hydroxychloroquine. Although these clinical findings are not pathognomonic of dermatomyositis, in the right clinical scenario, they are precious diagnostic tools.

KEYWORDS – Autoantibodies; Dermatomyositis; Drug Eruptions; Hand Dermatoses; Hydroxychloroquine/adverse effects; Ubiquitin-Activating Enzymes.

INTRODUCTION

Dermatomyositis (DM) is a rare idiopathic inflammatory myopathy with diverse cutaneous and systemic manifestations.¹ It can occur at any age, having a bimodal distribution – between 5 and 15 years old in the juvenile form and between 40 and 60 years old in the adult form –, and a higher prevalence in the female gender with a 2:1 female/male ratio.²

In the absence of the classical cutaneous findings and systemic symptoms, the diagnosis of DM can be challenging. Nevertheless, the use of the recently described myositis specific antibodies (MSAs) can aid in establishing an earlier diagnosis, promptly starting treatment and minimizing the risk of disease progression.^{3,4} Although the role of MSAs in the pathogenesis of DM remains to be completely determined, it is envisaged that these antibodies will aid in the subclassification of DM

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into homogenous clinical phenotypes and in the guidance of the treatment.^{3,4} It is known that pathophysiologic differences exist between autoantibody subsets in DM, leading to different clinicoserologic phenotypes, with variable prognosis and distinctive responses to treatment.⁴⁻⁶

Adverse skin reactions to hydroxychloroquine (HCQ), a standard first-line treatment in DM, have been reported and a strong association with anti-small ubiquitin-like modifier activating enzyme (SAE-1/2) antibodies was recently described.⁷

CASE REPORT

A 70-year-old caucasian woman presented with a three-month history of a skin rash, mainly affecting sun-exposed areas, and low-grade fever. She denied any difficulty combing hair, getting out of a seated position or swallowing, as well as changes in voice, cough, shortness of breath, or dyspnea

on exertion. She recalled a previous diagnosis of cutaneous lupus erythematosus (LE) made at another healthcare facility five years before. At that time, a trial of HCQ was initiated but soon interrupted due to a serious drug reaction, characterized by a generalized maculopapular blanching skin rash with palmoplantar and mucosal involvement. Recent treatment with methotrexate (maximum dose of 10 mg weekly, due to gastrointestinal intolerance) was ineffective after three months.

On physical examination, heliotrope and a photodistributed scaly erythematous rash of the upper trunk and limbs were present with a V distribution on the anterior chest (V sign), and the shawl, sleeve, and holster signs. Gottron's papules and Gottron's sign of the extension surface of the metacarpophalangeal and proximal interphalangeal joints of the hands, elbows, and knees, were also documented. The dorsal (Fig. 1A) and lateral (Fig. 1B) aspects of the



Figure 1 - Cutaneous findings on the hands at the time of diagnosis. (A) - Erythematous, hyperkeratotic and slightly scaly papules - Gottron's papules - and plaques on the dorsum of the digits with ragged cuticle/cuticular hypertrophy and periungual erythema. (B) - Hyperkeratotic, scaly and fissured lesions on the lateral surface of the digits, particularly on the ulnar side of the thumb and radial side of the other fingers - mechanic's hands.

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fingers were hyperkeratotic, scaly, and fissured – mechanic's hands –, with ragged cuticle and periungual erythema. The remaining physical examination, namely the cardiopulmonary auscultation and neurologic exam, was unremarkable.

Laboratory examination revealed low titer antinuclear antibodies positivity (1/80) and a strong positivity for anti-SAE-1/2 antibodies was documented by immunoblotting (Euroline® Autoimmune Inflammatory Myopathies 16Ag). Anti-dsDNA, anti-Ro52/60, anti-La, anti-Sm, anti-RNP-Sm, anti-Scl-70, anti-PM-Scl-75/100, anti-Ku, anti-SRP, anti-NXP2, anti-MDA5, anti-TIF1g, anti-Mi-2a/b, and antisynthetase (anti-Jo-1, anti-OJ, anti-EJ, and anti-PL-7/12) antibodies were negative. A skin biopsy revealed an interface dermatitis with basal cell vacuolization, apoptotic keratinocytes, and perivascular lymphocytic infiltrate. There was no evidence of muscle involvement (serum creatinine kinase, myoglobin and aldolase levels within the normal range and electromyogram without changes), interstitial lung disease (normal chest computed tomography and lung function testing) or underlying solid or hematologic malignancy. As such, a diagnosis of amyopathic DM was made. The Cutaneous DM Disease Area and Severity Index (CDASI) total activity score (range 0-100) at the time of diagnosis was 40 (moderate to severe disease).⁸

The patient was initially treated with medium to high-dose systemic glucocorticoids (SGC; up to 0.5 mg/kg daily, 40 mg of prednisolone), azathioprine (up to 1 mg/kg daily, 75 mg), topical betamethasone ointment (0.5 mg/g twice daily) and strict photoprotection with the use of broad-spectrum sunscreen (sun protective factor of at least 50). Treatment with high-dose SGC induced diabetes mellitus, so the dose was tapered to 20 mg daily, and azathioprine had to be stopped two months later due to hematologic and hepatic toxicity. At this point and with disease relapse, mycophenolate mofetil (2000 mg daily) was started, initially associated with intravenous immunoglobulin (IVIg; 2 mg/kg monthly). After a 12-month period under the aforementioned treatment, the patient persisted with moderately active disease (Fig. 2), CDASI of 22, and corticodependency (worsening of the skin lesions with less than 10 mg of prednisolone). Only after the association of intravenous rituximab (RTX; 2 g six-monthly) with mycophenolate mofetil a complete disease remission and gradual weaning of prednisolone were accomplished after the first cycle of RTX. One year later, the patient persists in clinical remission and without new symptoms or serious side effects from the current treatment.

DISCUSSION

Although the diagnosis of DM could be challenging, a physical examination alone usually leads expert clinicians to its suspicion and a correct diagnosis.⁹ In all cases, especially when the skin findings are not straightforward, a thorough and detailed skin examination is mandatory. Although not considered to be pathognomonic of DM, mechanic's hands are a precious diagnostic tool, enabling



Figure 2 - Cutaneous findings on the face and trunk before treatment with rituximab: periorbital edema with violaceous erythema of the face – heliotrope rash – and of the anterior upper chest – V sign.

a correct and prompt differential diagnosis.⁴ Classically described in patients with the antisynthetase syndrome, they can be found in patients with DM associated with other MSAs and with other autoimmune diseases like LE.^{4,6} Actually, before the correct diagnosis of amyopathic DM, our patient had a previous clinical diagnosis of LE, which illustrates the difficulty in distinguishing between these two entities. In addition to the presence of mechanic's hands, this patient presented other clinical findings that led to a probable diagnosis of DM, before complementary studies – the existence of other typical cutaneous lesions and a history of previously documented adverse skin reaction to HCQ. Regarding this latter aspect, adverse skin reactions to HCQ have been previously reported as common in patients with DM, particularly when associated with anti-SAE-1/2 antibodies – approximately 4-fold increase in risk compared to those without this antibody.⁷

In DM it is important to timely install appropriate treatment and most patients do not respond to isolated skin directed therapies and will require systemic therapies.⁹ Antimalarials have been the preferred initial treatment for cutaneous DM due to their photoprotective and

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anti-inflammatory mechanisms.⁹ In this patient, the reinroduction of HCQ was not considered to be a reasonable option, according to the clinical aspects of the drug eruption and immune profile, although cases of HCQ rechallenge are well documented in the literature, particularly in those with previous mild drug eruptions.¹⁰ SGC and IVIG are sometimes used for severe and refractory cutaneous DM, as a transition therapy until the effect of other systemic immunosuppressant drugs is documented.^{9,11} In the absence of high-quality evidence for the use of immunosuppressive therapy, the choice of the primary agent depends on the personal physician's experience and the patient's comorbidities and co-medication.^{9,11} If the disease is refractory to standard immunosuppression and IVIG, treatment escalation to RTX or cyclophosphamide can be considered, as in the presented case. Although there are a lack and conflicting results supporting the use of RTX for cutaneous disease, a large prospective, randomized controlled trial (RIM trial) revealed a beneficial effect, in a post hoc analysis.¹²

Overall this case highlights the importance of non-classical clinical findings, namely mechanic's hands and a history of drug eruption to HCQ, for the diagnosis of DM, while providing insights regarding subclassification according to the associated MSAs and treatment in refractory cases.

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