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Therapeutic options in refractory anti-MDA5 dermatomyositis triggered by SARS-CoV-2 infection

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ABSTRACT

Anti-MDA-5 dermatomyositis (DM) is a rare disease subtype characterized by rapidly progressive interstitial lung disease alongside skin, vascular and visceral involvement. The severity of the pulmonary disease is corelated with a weaker prognosis.

A 31-year-old female patient was admitted for hand arthritis, upper girdle pain and multiple erythematous papular facial lesions on the face, digital ulcerations and Raynaud's. The symptoms started immediately after the onset of the SARS-CoV-2 infection.

Positive anti-MDA5 and anti-centromere antibodies were identified, thus amyopathic DM - CREST syndrome overlap diagnosis was placed.

Due to pulmonary involvement, corticosteroids, immunomodulatory drugs (mycophenolate mofetil, hydroxychloroquine, cyclophosphamide) were initiated, with no clinical benefits. Lack of response led to initiation of rituximab, oral tacrolimus and nintedanib with no apparent progression of the disease. Refractory cases require escalation of the standard therapeutic approach. SARS-CoV-2 infection can represent a trigger of autoimmunity in DM which needs to be further assessed.

Keywords: amyopathic dermatomyositis, SARS-CoV-2, refractory, interstitial lung disease

INTRODUCTION

Anti-melanoma differentiation-associated protein-5 (MDA-5) dermatomyositis (DM) is a distinct clinical subset of adult-onset DM that affects around 5-10% of the DM patients and is characterized by skin involvement (heliotrope rash, Gottron's sign, ulcerations), arthritis and rapidly progressive interstitial lung disease (RP-ILD), the latter affecting half of the patients (Sterling West, 2019). In its course, DM can associate Raynaud's phenomenon, subcutaneous calcifications, cardiac and gastrointestinal manifestations but the RP-ILD remains responsible for the poor prognosis of this phenotype, considering the heterogenous response to therapy.

An important aspect of anti-MDA-5 DM is that infections have been previously recognized as main triggers of the disease and recent cases have raised awareness related to its association with SARS-CoV-2 infection (Sampaio et al., 2021).

Although there is limited data about the possible correlation between COVID-19 and the host immune response, we report a case of MDA5-DM developed within days after onset of SARS-CoV-2 infection. This is aimed to support further research into autoimmunity triggered by viruses.

Moreover, the case presentation emphasizes the importance of prompt diagnosis within a multidisciplinary approach. Aggressive, severe pulmonary involvement imposes immediate therapeutic management and if proven refractory to classical treatment, laying all cards on deck can sometimes be the sole rescue for the patient.

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CASE PRESENTATION

A 31-year-old female patient, with no prior significant medical history addressed the Rheumatology department for the first time in June 2021, complaining of pain and swelling of the small joints of the hands, elbows and shoulders, accompanied by multiple erythematous papules on the face and arms (Figure 1 and 2).

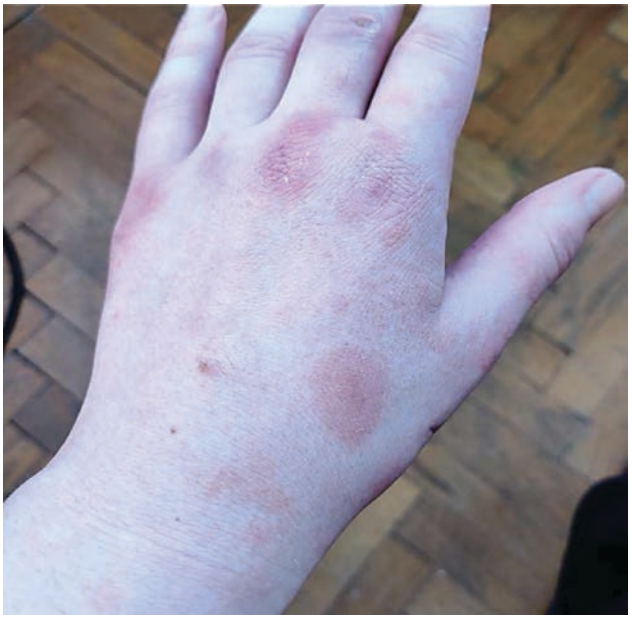

FIGURE 1. Peripheral edema and rash of hands. Gottron's sign on the dorsal surface of the interphalangeal and metacarpophalangeal joints

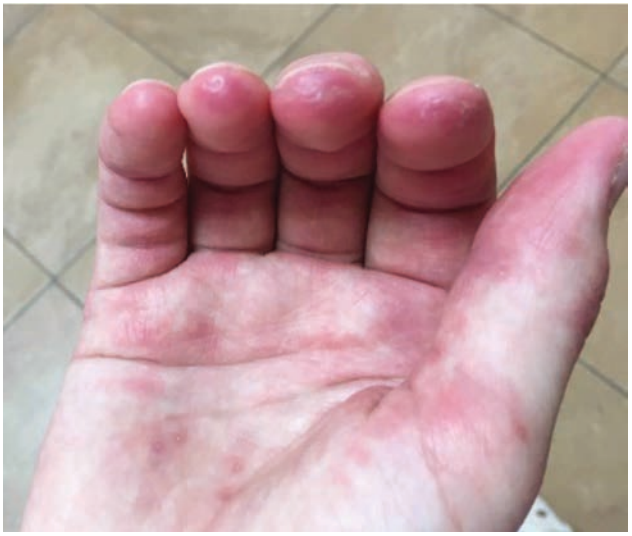

FIGURE 2. Digital ulceration and palmar rash

Patient describes the onset of symptoms shortly after being positive for COVID-19 for which no hospitalization was required. Soon, periorbital edema and heliotrope rash appeared; arthralgia of the small joints of the hands soon followed.

Multiple diagnoses were considered at the time by consulting physicians, namely rheumatoid arthritis, thus corticosteroids were initiated at a maximum dose of 32 mg/day that was gradually tapered. However, the patient experienced a relapse in symptoms shortly after corticosteroids were interrupted, so methotrexate 10 mg weekly was started, with no significant clinical improvement.

Follow-up physical examination maintained the Gottron's sign changes on the dorsal surface of the interphalangeal and metacarpophalangeal joints (Figure 1) and accentuated rash over the extensor surface of the elbows. Also, a shawl-like rash was noted, together with a round ulceration on the right elbow (Figure 3) and nailfold erythema (Figure 4). Patient also described recurrent oral ulcerations and skin color changes highly suggestive of Raynaud's phenomenon. Despite extensive cutaneous involvement, patient exhibited no muscle symptoms.

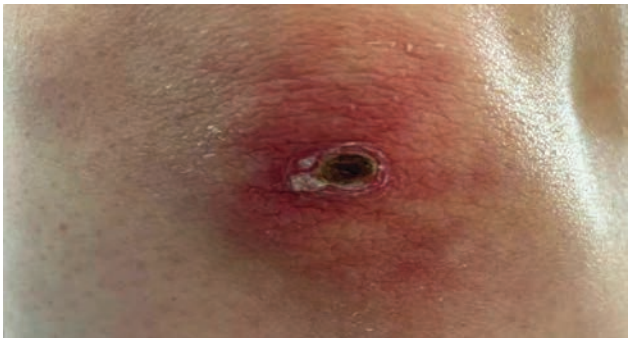

FIGURE 3. Gottron's and ulceration on the extensor surface of the elbow

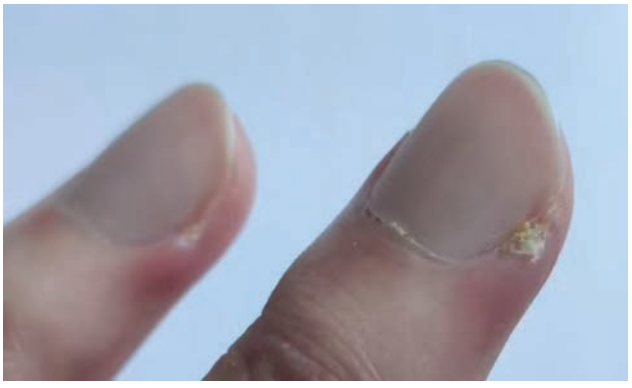

FIGURE 4. Nailfold erythema

Initial workup in our department revealed minimally elevated inflammatory markers (erythrocyte sedimentation rate, ESR, C-reactive protein, CRP), mild lymphopenia and within-range muscle enzyme levels (creatin kinase, CK, lactate dehydrogenase, LDH, alanine and aspartate aminotransferases, ALAT, ASAT).

The immunological testing confirmed a strongly positive presence of anti-MDA5 and anti-Mi-2 alpha autoantibodies. Moreover, anti-Ro52 antibodies and anti-SS-A were positive. Rheumatoid factor (RF), antinuclear antibodies (ANA), anti-U1RNP and dsDNA antibodies were negative.

Considering the clinical setting and the immunological investigations, the diagnosis of adult-onset DM was established. Given the frequent association of RP-ILD with the anti-MDA5 subset of disease, a chest HR-CT scan was performed. Multiple, bilateral pulmonary nodules were described, together with post-COVID sequelae lesions. Ventilatory function tests were normal.

Methylprednisolone was reinitiated at a dose of 40 mg daily with slowly decreasing doses over a period of four months together with hydroxychloroquine (HCQ) 400 mg/day and mycophenolate mofetil (MMF) titrated up to 2 grams per day. Initial clinical response was favorable, with partial resolution of the rashes and ulcerations but a symptoms' rebound occurred at corticosteroid tapering. The patient additionally described muscle weakness and exertion fatigue, while the physical and laboratory exams showed no supplementary changes.

Nailfold capillaroscopy highlighted a moderately reduced capillary density and numerous changes in the morphology and apical diameter of the vessels. Scattered mega capillaries and numerous hemorrhages were observed, indicating a scleroderma-like pattern. Thus, the dose of mycophenolate mofetil was increased to 3 grams daily, adding calcium channel blockers and nitroglycerin ointment. Corticosteroids were further used at low doses.

Despite continuous therapeutic immunosuppression, the clinical manifestations did not improve. Further immunological tests revealed high titers of anti-centromere antibody, adding to the presence of Raynaud's, calcinosis so that the diagnosis of amyopathic DM and CREST overlap syndrome was formulated.

MMF was replaced with intravenous Cyclophosphamide (CYC) and Bosentan 250 mg/day was added in December 2021. A number of six CYC cycles with urinary bladder protection were administered but the patient developed a generalized allergic reaction to Mesna with intense rash and periorbital edema. Infusions of Vasaprostan were administered for digital ulcerations and topical tacrolimus was used for facial rash, with mild favorable response.

Fatigue and dyspnea on exertion became persistent so chest HR-CT scan was repeated in both November 2021 and May 2022. Increased dimensions of the subpleural areas of interstitial infiltrate were identified and six months later the imaging depicted bilateral pulmonary nodules, interstitial fibrotic lesions and global size progression of the pulmonary lesions. Spirometry tests performed in May 2022 detected diminished forced vital capacity (FVC) and reduced diffusing capacity of carbon monoxide (DLCO).

Considering the progression of the disease, therapy tailoring was imposed, and the patient was initiated on rituximab, oral tacrolimus and anti-fibrotic therapy with nintedanib. Up to this moment, the patient is clinically stationary, with good tolerance of the therapeutic scheme. A three-month follow-up will assess the benefits to this combo-therapy or if supplementation with intravenous immunoglobulins needs to be administered.

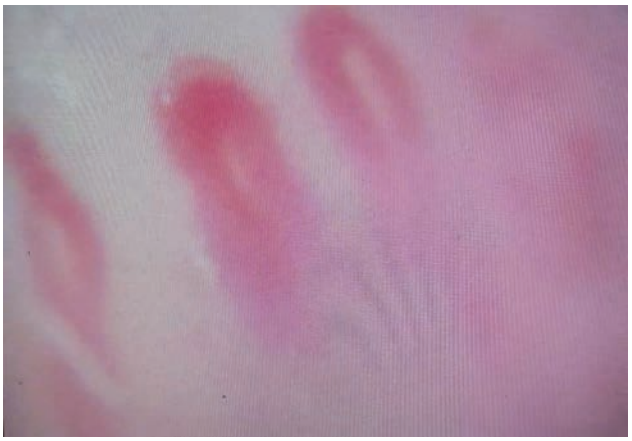

FIGURE 5. Scleroderma-like pattern in nailfold capillaroscopy

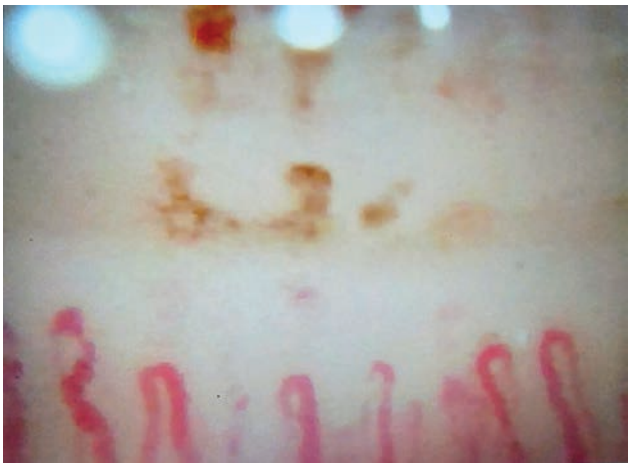

FIGURE 6. Numerous capillary hemorrhages and reduced capillary density

DISCUSSIONS

The present case highlights the clinical presentation and rapid progression of a rare and often misdiagnosed disease, anti-MDA5 clinically amyopathic DM overlapping with CREST syndrome. Placing the correct diagnosis might be challenging since the hallmark of classic myopathies, namely muscle involvement is absent, and the cutaneous manifestations can be misleading. Moreover, corticosteroid-induced myopathy should be carefully considered in the differential diagnosis.

Since pulmonary changes are closely linked to the disease outcome, intense focus should be on the therapeutic management. Literature describes as mainstay treatment for RP-ILD corticosteroids, immunosuppressives like cyclosporine, tacrolimus, cyclophosphamide or mycophenolate mofetil or biologics such as rituximab and tocilizumab.

In the present case, corticosteroids were administered in combination with immunosuppressive agents but with no significant clinical and imaging improvement. Cases refractory to similar therapy combination are estimated to have an overall mortality rate of 40%.

There is limited data on therapeutic options left at this point. The effectiveness of rituximab in anti-MDA5 DM with severe, refractory ILD has been evaluated only in case reports and small series, but some studies showed that 71.43% of patients responded to treatment (He et al., 2022). Other studies reported efficacy of JAK inhibitors (tofacitinib, ruxolitinib) in patients with severe disease relapses, since IFN-I pathway plays a key part in MDA5-DM. Plasmapheresis and intravenous immunoglobulins are used as rescue therapies and can be tempted in non-responsive phenotypes. Both are positively cited in small case series, but effectiveness in large cohorts needs to be assessed.

Anti-fibrotic treatment with nintedanib has recently been approved nationwide for progressive ILD in autoimmune diseases, so data regarding its efficacy is also limited (Kuwana et al., 2021).

The management of ILD is often difficult since the clinical course, treatment options and response are highly variable. Identifying patients at risk of developing lung fibrosis is essential. Moreover, early treatment seems to improve the prognosis (Muro et al., 2012).

In adult-onset DM, specific autoantibodies are related to specific clinical features and can predict disease outcome (Romero-Bueno et al., 2020). Anti- MDA5 are frequently associated with an aggressive evolution and rapid organ impairment and patients should perform imaging and respiratory functional tests even in the absence of symptoms (Y. Xu et al., 2016). Nonetheless, as is the patient's case, the association of anti-Ro52 with anti-MDA5 is suggestive for a more severe disease course (A. Xu et al., 2021). Other risk factors that have been identified as contributing to RP-ILD are skin ulcerations, high CRP, hyper-ferritinemia and lymphocytopenia (Y. Xu et al., 2016), (Carrasco et al., 2021).

Another point to consider is that multiple cases of anti-MDA-5 DM have been recently reported in connection with COVID-19 infection or vaccine administration. Cases of amyopathic DM triggered after exposure to SARS-CoV2 antigens with both positive anti-MDA5 and anti-Ro52 have been described. The pathogenic mechanism that links COVID-19 to DM onset still needs to be addressed (Gonzalez et al., 2022).

CONCLUSIONS

The present case illustrates the wide spectrum of clinical findings associated with idiopathic inflammatory myopathies and is intended to raise awareness of anti-MDA5-DM, which is a rare but challenging disease. Pulmonary involvement may represent a main organ target in choosing therapy. Rheumatologists need to establish a standard-of-care in refractory MDA5-DM cases with severe lung disease.

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