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Complete, refractory dysphagia in a dermatomyositis patient with positive anti-NXP-2 antibodies

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ABSTRACT

Dermatomyositis (DM) is a rare autoimmune disorder defined by weakness of the striated muscles and a distinctive skin rash. Dysphagia is a serious symptom that can be difficult to manage, severely impacting quality of life and long-term survival. The aim of this report is to highlight a case of an anti-NXP-2 positive DM with severe dysphagia refractory to multiple therapies, including steroids, cyclophosphamide and intravenous immunoglobulins. Anti-NXP-2 autoantibodies indicate a specific disease phenotype adding severe muscle weakness, dysphagia, peripheral edema and underlying malignancy.

Keywords: systemic lupus erythematosus, late-onset, elderly onset, serositis, arthritis

INTRODUCTION

Dermatomyositis (DM) is an inflammatory myopathy characterized by the presence of progressive, symmetrical weakness affecting the proximal skeletal muscles, associated with skin involvement, such as pathognomonic heliotrope rash or Gottron's sign and potentially abnormal nailfold capillaries. In its course, DM can associate arthritis, Raynaud's phenomenon, subcutaneous calcifications, cardiac manifestations or interstitial lung disease and gastrointestinal symptoms. The latter are mainly attributed to dysphagia, due to the involvement of the striated muscles of the upper esophagus (1,2).

An important aspect of DM is the frequent association with underlying malignancy, which affects about 20% of patients with adult-onset disease, with that percentage going up to 50% of those who develop the disease after the age of 65. Neoplastic disease can be present at the moment of diagnosis, or it can occur later, usually in the first 3 years following the onset of dermatomyositis, thus requiring repeated screening tests guided by patients' age, gender and clinical manifestations (1-3).

When confirming the DM diagnosis, serological tests are available which include myositis-specific autoantibodies. Their positivity might indicate the particular phenotype of the disease and potential outcome, since they associate with clinical manifestations in the idiopathic myopathy spectrum. The anti-NXP-2 antibodies are encountered in around 18-25% of adult DM and have a distinct disease presentation with myalgia, peripheral edema and severe dysphagia while exhibiting milder skin involvement. Moreover, despite being associated with ischemia in juvenile DM, in adult forms these specific autoantibodies should be linked to malignancy.

CASE PRESENTATION

A 66-year-old female patient with a known history of arterial hypertension and recently confirmed type II diabetes on insulin treatment, was admitted in the Rheumatology Department with significant symmetrical muscle weakness affecting the limbs, more accentuated in the upper girdle as well as the anterior flexors of the neck.

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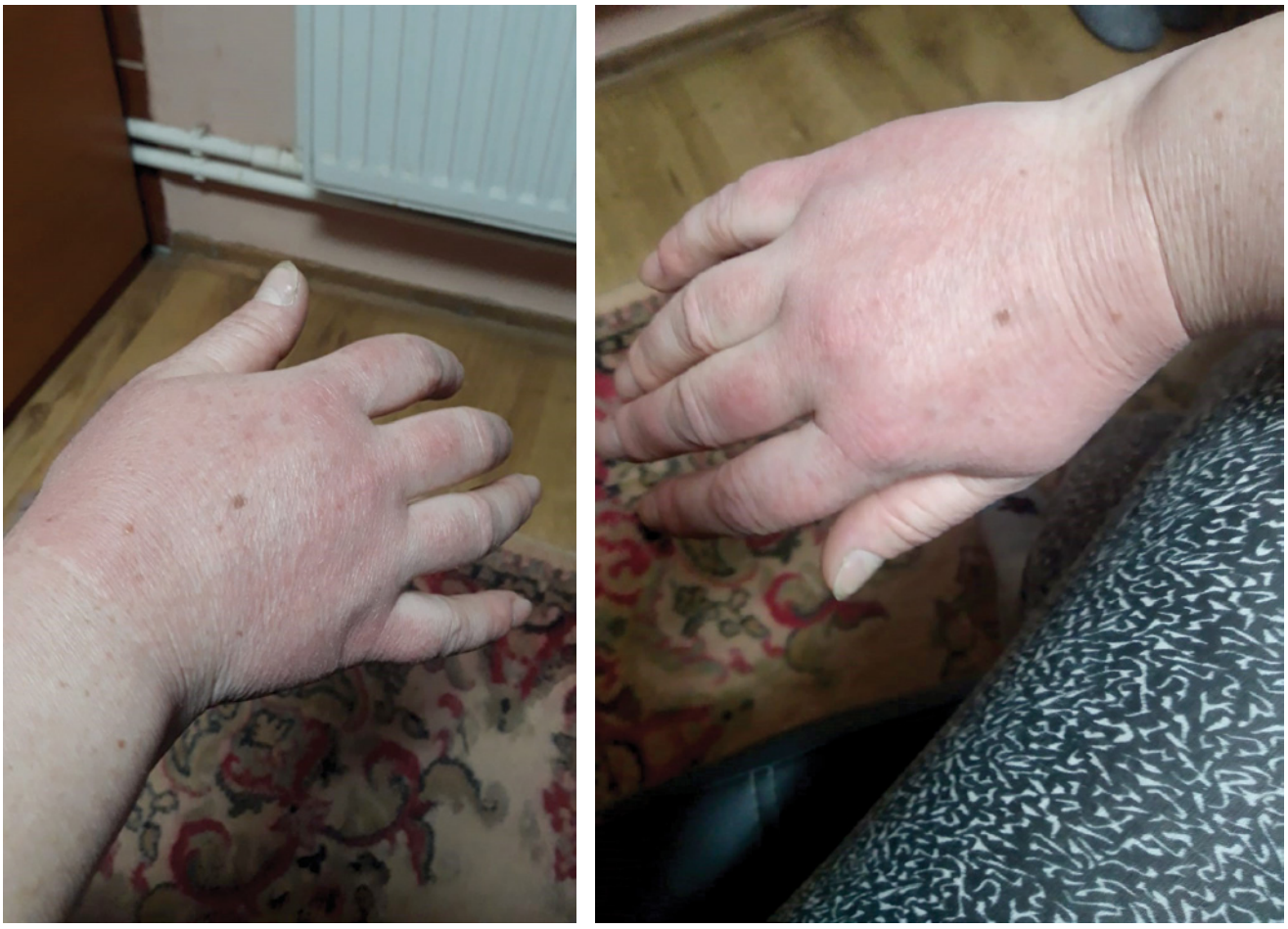

FIGURE 1. Peripheral edema and rash of hands (Gottron's sign)

Patient complained of fatigue and moderate weight loss in 3 weeks due to a mild degree of dysphagia for solid food intake.

A facial rash was noted upon admission which was distributed on the forehead, malar area and chin, hand rash suggestive of Gottron's sign and considerable peripheral edema of the upper limbs.

Further patient inquiry also revealed a history of Raynaud-like phenomenon that had never been evaluated by a specialist, dating for more than five years.

Laboratory testing revealed significantly high muscle enzyme levels (creatin kinase CK, lactate dehydrogenase LDH, alanine and aspartate aminotransferases ALT, AST), ranging from 10 to 30 times the laboratory reference value together with moderately elevated inflammatory markers (erythrocyte sedimentation rate, ESR, C-reactive protein, CRP).

Multiple diagnoses were considered at this point, thus further investigations were mandatory for a clearer clinical setting.

Patients' thyroid function was normal and *Trichinella spiralis*, hepatitis B, C, HIV infections were excluded based on the negative indicative tests.

Nailfold capillaroscopy highlighted numerous changes in the morphology and diameter of the capillaries, the presence of scattered mega capillaries, indicating a nonspecific pattern.

The delayed immunological testing showed high titer ANA (7-fold higher), with the myositis specific-antibody panel revealing strongly positive anti-NXP-2 and anti-Ro52 autoantibodies.

Orienting the diagnosis towards DM, a muscle biopsy was performed, revealing chronic inflammatory lymphoplasmacytic interstitial infiltrate, compatible with an inflammatory myopathy. Prior electromyography was unavailable at the time. Adding the clinical presentation (cutaneous, muscular and mild digestive involvement) to the laboratory and biopsy findings, the diagnosis of adult-onset idiopathic DM was established, in accordance with the Bohan and Peter classification criteria.

A comprehensive screening was performed in order to identify possible malignancies, including thoracic, abdominal and pelvic CT scans, tumoral marker testing, a thyroid ultrasound and gynecological and ENT examination, yet nothing of significance was found. Upper endoscopy and barium swallow test revealed no striking changes apart from mild gastritis.

Colonoscopy was avoided because of patient reluctancy to undergo the procedure.

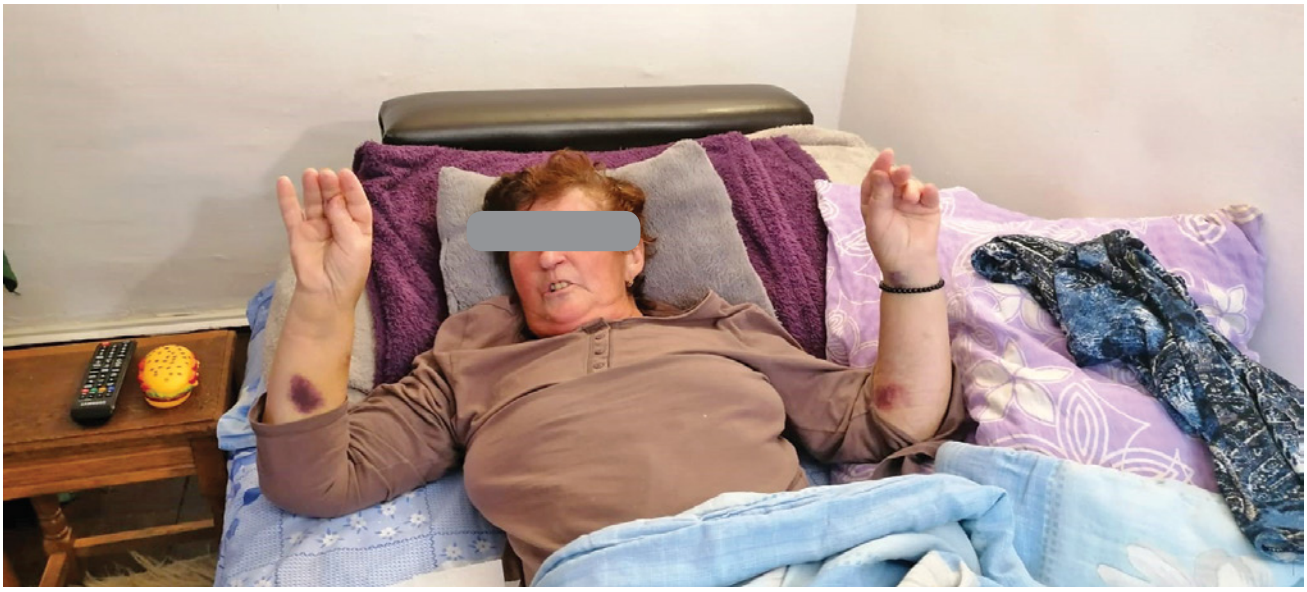

FIGURE 2. Absent mobility of the shoulder girdle and neck flexors

Given the significant muscle involvement and high-titer muscle enzyme values, pulse-therapy with methylprednisolone was administered followed by intravenous cyclophosphamide (CYC). Additional anticoagulant therapy was deemed necessary due to the patient's very limited mobility, adjustment of insulin therapy and early physical therapy sessions were conducted in order to help improve muscle function.

The initial clinical response was favorable, with the slight improvement of dysphagia, muscle weakness and fatigue, resolution of peripheral edema, while the biological response was even more encouraging, as a significant reduction in muscle enzyme levels was observed. The patient was discharged with the recommendation to continue oral glucocorticoid therapy and return for second round of CYC immunosuppression.

Two weeks later, the patient returned to the emergency room with aggravating complete dysphagia for both solids and liquids, dysphonia, persistent muscle weakness and extreme fatigue. Due to the severity of symptoms, placing a nasogastric tube was considered necessary in order to facilitate feeding and reduce the risk of choking and aspiration.

Reevaluation of causes for patient's dysphagia was imposed, thus a CT scan of the neck area and an ENT reevaluation including fibroscopy were performed but revealed no abnormal findings, except for abundant salivary stasis.

An esophageal manometry was performed despite patient's frequent cough reflex, indicating the absence of peristalsis in the esophageal body. Videofluoroscopic swallow study was unobtainable.

Considering the severity and life-threatening organ involvement, pulse steroid therapy was reinitiated together with a course of intravenous immunoglobulin (IVIG) therapy 1 g/kg. The combined therapy showed major biological improvement, with normalization of muscle enzymes within a week but no signs of clinical benefit were noted. The patient displayed no capacity of swallowing because of abundant sputum.

Persistency of severe, refractory dysphagia imposed placing a percutaneous endoscopic gastrostomy for enteral nutritional support with standardized formulas to keep a balanced normocaloric hyperproteic diet. The energy expenditure was estimated through the Harris Benedict formula and vitamin and trace elements were added.

Unfortunately, the patient was discharged upon request developing a depressive status despite in-hospital psychotherapy, leaving with minimal muscle recovery.

DISCUSSION

Establishing the diagnosis of DM was not highly challenging based on patient's clinical manifestations, serological data and histopathological confirmation.

However, notable features of this case include the particular phenotype associated with anti-NXP-2 antibodies, namely significant peripheral edema and severe dysphagia, resistant to glucocorticoids, cyclophosphamide and even intravenous immunoglobulins.

Dysphagia is present in a significant number of DM cases, with reports ranging from 10% up to an estimated 70% of patients developing this symptom during the course of the disease, with varying degrees of severity (4,5). It usually develops within the first year after diagnosis and it is more commonly associated with steroid-resistant forms of the disease (6). A 2016 study of 92 Japanese DM patients

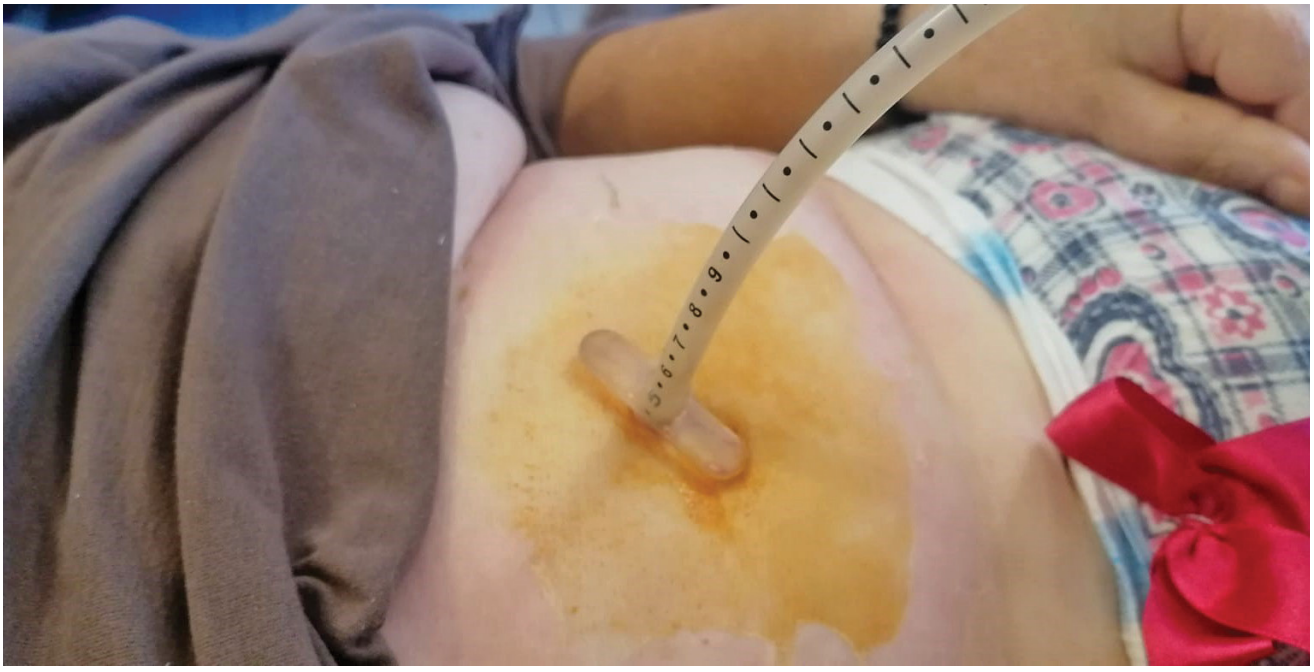

FIGURE 3. Placement of percutaneous gastrostomy tube

found that dysphagia was more frequent in elderly or male patients and it was more often associated with internal malignancy and anti-TIF-1γ antibody positivity, yet rarely with interstitial lung disease (7).

According to another study published in 2017 which included 253 patients with DM, anti-NXP-2 autoantibodies were correlated to subcutaneous edema and severe muscle weakness, as was the case with our patient. They also presented an increased risk of developing neoplastic disease. It seems that these specific myositis antibodies contribute to the dysphagia through reduced pharyngeal contractility (8-10).

Furthermore, a 2020 meta-analysis on the impact of dysphagia in idiopathic inflammatory myopathies concluded that the presence of anti-NXP-2 antibodies and malignancy were important risk factors in the development of dysphagia, while association with interstitial lung disease was once again rarely reported (11,12).

It is worth noting that both NXP-2 and TIF-1 proteins are involved in oncogenesis, with NXP-2 in particular being a key component in the activation of the p53 tumoral suppressor gene. It is therefore likely that these two autoantibodies could develop as a result of the antitumor immune response (13).

Other reported risk factors for the development of cancer in dermatomyositis patients are age over 60 at diagnosis, rapid disease onset of less than four weeks and diabetes. Repeated cancer screenings are recommended for patients with no detectable malignancy at diagnosis, since neoplastic disease can develop later, especially in the first three years of illness. The most frequently reported cancers occurring in DM patients are those affecting the breast, lungs, digestive tract, bladder, nasal cavity, throat, as well as Hodgkin's lymphoma (3).

Therapeutic options are limited and with a higher rate of failure in severe DM, steroid therapy usually being the first course of action (14). Cyclophosphamide and intravenous immunoglobulin therapy have been proven to be efficacious in a few of these cases (15,16). The recommended dose for IVIG trial is up to 2g/kg, depending on patients' response to therapy.

Myositis can also benefit from off-label biological therapies, which have proven partially satisfactory results in randomized, double-blinded, placebo-controlled studies or in open-label analysis. These therapies can target tumor necrosis factor (TNF)-alpha, interleukin IL-1, 6 or B-cells like rituximab (17).

Non-pharmacological strategies might be available in selected centers aiming to improve symptoms of cricopharyngeal dysfunction. Procedures like injection of botulinum toxin A in the cricopharyngeus muscle, cricopharyngeal dilatation or cricopharyngeal myotomy have been described (11).

DM is associated with higher morbi-mortality rates, since most patients have either a chronic continuous or a polycyclic course of illness. Overall, age over 50 at disease onset, dysphagia and anti-NXP-2 antibody positivity are factors associated with a poor long-term outcome (18-20). Moreover, the survival rate of patients with severe dysphagia requiring percutaneous endoscopic gastrostomy is reported to be low despite adequate treatment.

CONCLUSIONS

DM is encompassed in the idiopathic inflammatory myopathies. Among classical manifestations,

dysphagia represents a serious and often difficult to control symptom, leading to reduced long-term survival. The presence of anti-NXP-2 antibodies add to the poor prognosis. Regular cancer screening is recommended in these cases, as neoplastic disease can be undetectable at the moment of diagnosis.

Despite the great strides that have been in the management of DM, the treatment of patients presenting with severe, refractory dysphagia remains a challenge. Immunomodulatory therapies are to be administered and assess the effects on swallowing function. Further research is necessary in order to determine the best course of action in managing these difficult and often life-threatening cases.

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