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Case Report

From how many Angles Should Immune-Mediated Necrotizing Myopathy be Observed?

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Abstract:

Idiopathic inflammatory myopathies (IIM) are a heterogeneous group of autoimmune diseases characterized by inflammation of skeletal muscle causing proximal weakness. The clinical case describes a 72-year-old male patient with proximal quadriparesis for 3 months, associated with constitutional syndrome. Analyzes with rhabdomyolysis and positive anti-SRP antibody. Biopsy findings compatible with immune-mediated necrotizing myopathy. The complementary study revealed a laryngeal neoplasia. The patient refused treatment and died 6 months after diagnosis.

Keywords: idiopathic inflammatory myopathy; immune-mediated necrotizing myopathy; myopathy specific antibodies; anti-SRP; anti-HMGCR

Introduction

Idiopathic inflammatory myopathies (IIM) are an heterogeneous group of autoimmune diseases characterized by skeletal muscle inflammation and proximal muscle weakness. They can affect other organs and systems such as the skin, lungs, gastrointestinal tract and joints.[1] IIM are divided into different subtypes: dermatomyositis, polymyositis, inclusion body myositis and immune-mediated necrotizing myopathy (IMNM). Initially, the subdivision focused mainly on clinical and histological findings.[2] However, it was often limited by clinical and histological overlap between the various myopathies. Thus, specific and sensitive antibodies for myositis emerged, which, in addition to overcoming this diagnostic limitation, have become essential in the approach to IIM. Specific antibodies are exclusive to myopathies while sensitive antibodies, despite being present in more than 50% of cases, can be found in other diseases. Antibodies are associated with the immunopathogenesis of IIM, defining different clinical and histological phenotypes, predicting the trigger and prognosis in question.[2, 3, 4]

Case Description

A 72-year-old man went to the emergency department due to muscle weakness in the lower limbs, which had been progressively worsening for 5 months. Since the beginning of the condition with a weight loss of 20%. On objective examination, he appeared emaciated, with quadriparesis of proximal predominance. According to the Medical Research Council (MRC) muscular strength classification, he had proximal muscular strength in the upper limbs grade 1, distal 3 bilaterally; in the lower limbs (LL) with grade 1 proximal and grade 3 distal strength, bilaterally and marked amyotrophy; limitation of trunk extension, osteotendinous reflexes and preserved sensitivity, without other changes on neurological examination; no notion of dysphagia or dysphonia; no skin or joint changes. This was a patient with a personal history of chronic obstructive pulmonary disease and a smoking history of 53 pack-years. Analysis with liver cytolysis with GOT 385 IU/L, GPT 244 IU/L and rhabdomyolysis with creatine phosphokinase (CPK) of 11367 IU/mL, myoglobin of 7321 ng/mL, aldolase elevation (62.7 U/mL). He underwent a complementary study with high-resolution computed tomography (CT), transthoracic echocardiography and magnetic resonance imaging of the dorso-lumbar spine without relevant changes; normal thyroid function, without complement consumption; ANA negative, specific antibodies associated with myositis, anti-SRP (signal recognition particle) positive, electromyography of LL with non-specific motor neuropathy; muscle biopsy compatible with inflammatory myopathy: numerous atrophied fibers with rounded contours, dispersed throughout the fascicles; frequent fibers in necrosis and some in the process of myophagocytosis; focal endomysial fibrosis; inflammatory infiltrate located in the endomysium, perivascular. The combination of clinical findings, rhabdomyolysis, anti-SRP and histological results made the diagnosis of IMNM. Prednisolone 1 mg/kg (50 mg/day) and human immunoglobulin G (IgG) 0.5 g/kg for 5 days were started, with no response. A paraneoplastic study was carried out with thoraco-abdomino-pelvic CT (TAP), upper and lower digestive endoscopy, prostate specific antigen, without changes. The cervical ultrasound revealed a hypoechogenic mass measuring 4.2 x 2.5 cm, heterogeneous, hypervacularized, suggestive of laryngeal neoplasia. He was referred to otolaryngology where he underwent a biopsy with the

diagnosis of pharyngolaryngeal squamous cell carcinoma, stage cT3 N2c M0. Surgery and tracheostomy were proposed, which the patient refused. The disease progressed with worsening tetraparesis and consumptive syndrome. He died 6 months later following aspiration pneumonia.

Discussion

IMNM is the second most common myopathy, corresponding to 20% of IIM cases.[5] It is distinguished from other IIM by presenting a marked increase in CPK, 10 to 50 times the normal value, and pauci-extramuscular involvement. It manifests itself acutely to subacutely, the evolution is usually rapid and severe and is characterized by a poor response to immunosuppressive therapy.

There are 3 subtypes of MNIM. The first are associated with myositis-specific antibodies (MSAs): anti-HMGCR (hydroxy-3-methylglutaryl coenzyme A reductase) and anti-SRP. The third subtype is seronegative. The anti-HMGCR antibody is identified in 60% of cases and of these, 30-60% had previous exposure to statins. The pathophysiological mechanism is not completely understood, but there appears to be a genetic predisposition associated with the HLA DRB1*11:01.5,6 allele. Anti-SRP is present in 10 to 20% of IMNM cases and is more common in females. In anti-SRP cases, dysphagia is present in half of patients at the time of diagnosis and less than 20% of cases have cardiac involvement.[1,6] It is associated with interstitial lung disease (ILD), present in 10 to 25% of patients anti-SRP positive, while in anti-HMGCR patients, IDL is described in less than 5% of cases.[1]

Histologically, IMNM is predominantly characterized by the presence of necrotic myofibers dispersed to varying degrees, moderate and mainly focal upregulation of major histocompatibility complex class I.[1,6] Both SRP and HMGCR are expressed in the sarcolemma of regenerating muscle fibers. The respective antibodies can bind to their antigen and thus cause complement-induced muscle damage. Histologically, there is a deposition of complement C5b-9 in the sarcolemma.[3] Necrotic fibers are invaded and surrounded by macrophages to clean cellular debris. In anti-SRP and anti-HMGCR, there is usually no invasion of non-necrotic fibers by CD8+ cytotoxic T cells and muscle fibers are rarely surrounded by T cells.[5,6]

Although the pathophysiological mechanism is not completely known, it is known that 1 in 4 patients with IIM is diagnosed with a neoplasm within 3 years, especially in the year before and after the diagnosis. This risk is often associated with age, male sex, dysphagia, severity, skin ulceration and anti-TIF1γ antibody. [5,6,7]

The most diagnosed neoplasms in IIM are those of the lung, breast, ovary and lymphoma.[6] MSAs help to categorize patients according to neoplastic risk and some also correlate with different types of neoplasia.[5] This does not happen in IMNM or with the respective antibodies, anti-SRP and anti-HMGCR. Although seronegative cases and anti-HMGCR cases present a greater number of neoplasms, MNIM do not appear to have neoplasia as a trigger and are not related to a predominant type of cancer.[1,3,5,6] Therefore, neoplastic screening is not always linear and in this sense, some authors suggest dividing patients into 3 groups, according to neoplastic risk: low, moderate and high. In the first group, it is recommended to carry out an analytical study, chest x-ray and neoplastic screening according to age and individual factors; moderate risk, in addition to TAP CT, transvaginal ultrasound in women and testicular ultrasound in men under 50 years of age; high risk, positron emission tomography (PET). Patients should be reevaluated regularly with annual screening according to the complaints and indications mentioned above, preferably during the first 3 years of follow-up. High-risk patients should also undergo CT or PET annually.[6,7,8]

According to the IMNM, the patient presented is initially included in the moderate risk group. However, there are individual factors such as gender, advanced age and above all smoking that increase this risk and have included laryngeal neoplasia in the list of diagnoses to be screened for.[8]

Regarding treatment, current recommendations are based on observational studies and expert opinion.1 Therefore, it is suggested that IIM treatment should be personalized according to the patient's characteristics, subtype and evolution of the myopathy itself. Corticosteroid therapy is the basic therapy for myopathies, being the first treatment to be carried out at the time of diagnosis. Prednisolone is recommended at a dose of 1 mg/kg per day. Weaning from corticosteroid therapy should be gradual according to the patient's progress. [1,4] Immunomodulatory therapy associated with corticosteroid therapy varies, from IgG, through methotrexate, azathioprine to biological therapy such as rituximab.[1,4]

Compared to other myopathies, in IMNM there is diffuse muscular atrophy, edema and replacement by fat earlier and regardless of the time of disease evolution. These changes are more marked in anti-SRP patients, characterized by a severe course and therapeutic refractoriness, where early treatment with rituximab is associated with a more favorable response.[1]

In patients with IIM and especially in IMNM, the importance of motor rehabilitation is also highlighted, essential for the patients' functional recovery and associated treatment of the myopathy trigger, when identified.[1,4,7] However, despite severe immunosuppressive therapy and rigorous rehabilitation, MNIM is recurrently characterized by being a progressive, refractory and relapsing disease. Two years after treatment, 52 to 66% of cases do not experience complete neurological recovery.[9]

The management of IIM constitutes a clinical challenge, from diagnosis, therapy and follow-up. This clinical case demonstrates the acute and severe course of IMNM, a challenging diagnostic investigation and a treatment that fell short of the expectations of the medical team. A clinical history already with a poor prognosis per se, without motor rehabilitation and without treatment of the “trigger”, led to an unfavorable outcome.

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