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Severe myopathy in a patient with chronic neurological disease – diagnostic challenges

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ABSTRACT

Polymyositis is a rare disease that belongs to the idiopathic inflammatory myopathies (IIMs) group, characterized by chronic muscle inflammation, and in rare cases a life-threatening condition due to extra-muscular involvement.
Even though steroids constitute the building block of treatment of this disease, in severe cases, escalation treatment should be considered in order to obtain good clinical outcomes.
We report a clinical case of a 22-year-old female who developed progressive severe systemic muscular weakness, dysphagia and dysphonia, accompanied by elevated serum muscle enzymes, positive myositis-specific antibodies, and muscle biopsy suggestive of inflammatory myopathy. The clinical features and laboratory results led us to the diagnosis of polymyositis. On additional laboratory tests the patient tested positive for *Borrelia burgdorferi* (*Borrelia b*) specific antibodies. Due to life-threatening organ involvement the immunosuppressive treatment, immunoglobulin intravenous infusion and pulse therapy with methylprednisolone were initiated and she needed nasogastric tube in order to be fed. Furthermore antibiotic treatment was administrated. The patient improved almost completely after 3 months of treatment.

Keywords: polymyositis, immunosuppressive, Cyclophosphamide

INTRODUCTION

Idiopathic inflammatory myopathies (IIMs) are a rare, heterogeneous group of diseases characterized by chronic muscle inflammation and often extra-muscular findings, such as in the skin, lungs, joints. Polymyositis is a rare disease that belongs to IIMs, that demonstrates a diminished incidence among individuals younger than 20 years old, with a range of onset between 30 and 60 years old and affects more women than men. Clinical features of PM include symmetrical proximal muscle weakness of the upper and lower extremities [1,2]. Less common and sever cases PM can present with gastrointestinal involvement-dysphagia, constipation, cardiac involvement-dyspnea, Raynaud's phenomenon and arthritis due to joint involvement [3].

Polymyositis (PM) is an autoimmune disease which develops due to abnormal activation of cytotoxic T lymphocytes (CD8 cells) and macrophages against muscular antigens and the strong extrafusal muscular expression of major histocompatibility complex I causing damage to the endomysium of skeletal muscles [4,5] Interleukins and tumor necrosis factor (TNF) are cytokines involved in the pathogenesis of rhabdomyolysis. The exact etiology of the PM is unknown. It primarily affects individuals who already have an underlying systemic disease resulting from viral and bacterial infections, malignancies, or other autoimmune disorders. The human T-lymphotropic virus type 1 (HTLV1), human immunodeficiency virus (HIV) and hepatitis C virus are the primary viruses responsible for polymyositis [6-8].

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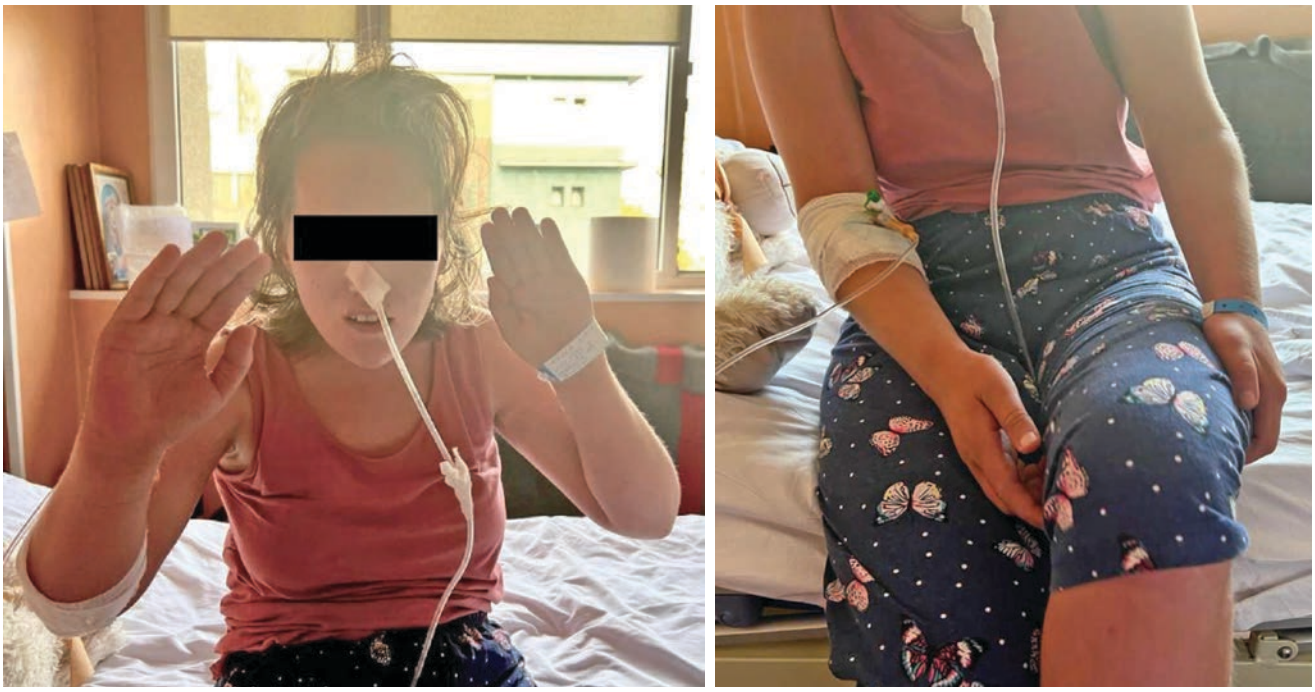

FIGURE 1. - Severe muscle weakness affecting the proximal part of the limbs

Lyme disease (LD) is a zoonotic disease caused by the gram-negative bacteria *Borrelia b. sensu lato.* LD may present with a wide range of clinical manifestations including symptoms of muscular, articular, nervous and cardiac involvement [9]. These symptoms being typical for many autoimmune diseases, such as PM.

The interference of the two conditions in clinical practice is rare and of considerable interest in view of the need to determine the right management approach.

CASE REPORT

In October 2022, a 22-year-old female, was referred to our rheumatology department with severe, rapid onset, over the last 2 weeks, muscle weakness, severe dysphagia, dyspnea, palpitations and involuntary weight loss (10 kgs in 3 weeks). She had no fever or other signs of recent systemic infections. She had not been exposed to toxic environment or new medications. She had a neurological history of epileptic encephalopathy and global development delay, for which she was under chronic treatment with levetiracetam. From her medical history we noticed an emergency department referral for a tick bite, years earlier. She wasn't tested for *Borrelia b.* infection, and she hasn't received any antibiotic treatment.

The patient's physical examination was remarkable for severe muscle weakness affecting not only the proximal part of the limbs but also the cervical musculature, respiratory muscles, including diaphragm leading to orthopnea, and bulbar musculature, causing severe dysphagia and dysphonia (Figure 1).

Tachycardia was also present. On skin examination Raynaud's phenomenon and livedo reticularis were observed on both lower limbs (Figure 2).

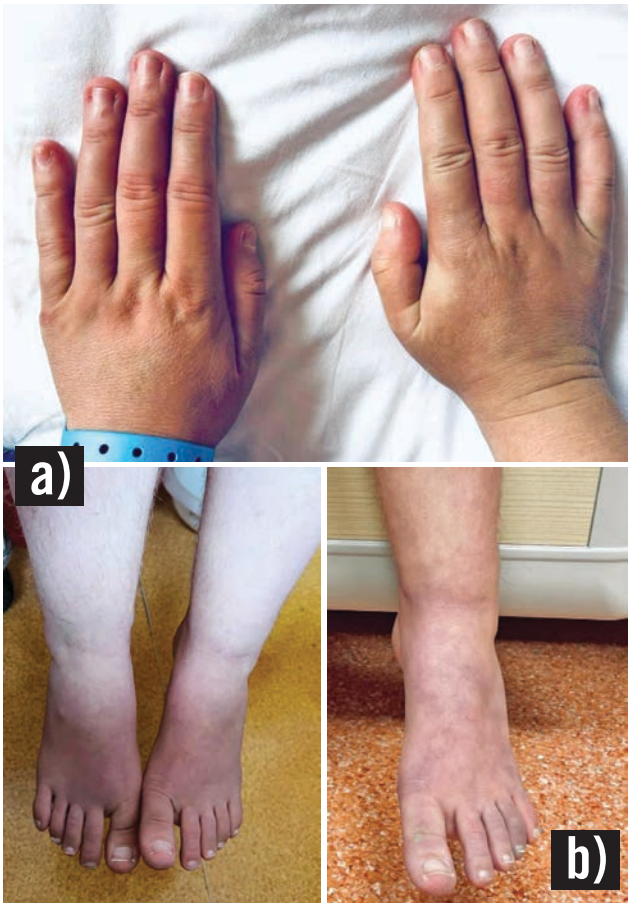

FIGURE 2. - a) Raynaud's phenomenon, b) livedo reticularis

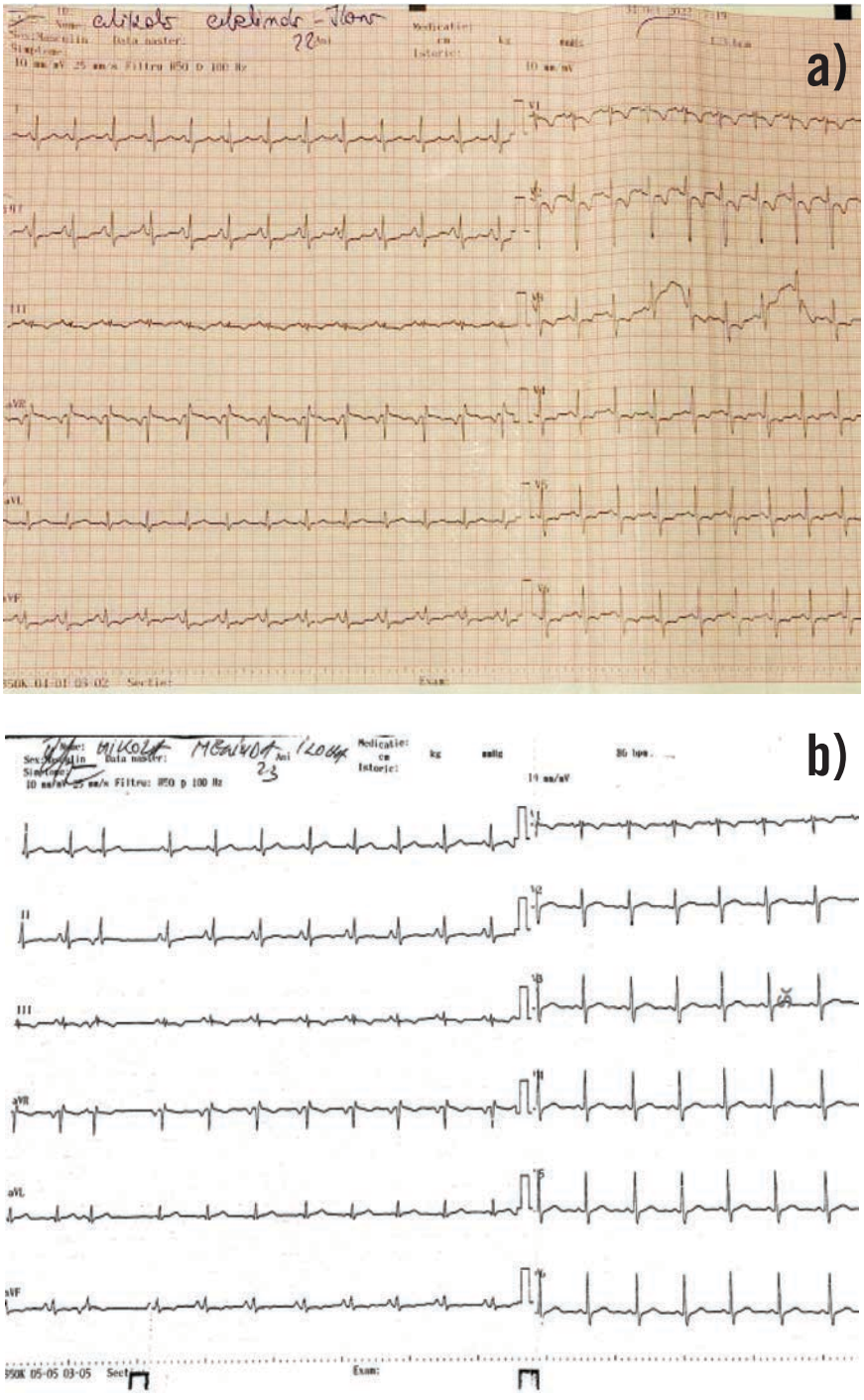

FIGURE 3. - a) EKG at admission; b) EKG at 3 months after admission

The rest of the physical examination was unremarkable.

Six months before admission, patient was referred to multidisciplinary departments, including rheumatology, for migratory arthritis and periorbital oedema. The immunological assays found positive ANA antibodies but was negative for myositis autoantibodies. The inflammatory markers were also negative. After one month of oral steroid treatment, she recovered completely.

On admission to our department, laboratory investigations showed a 50-fold elevation of plasma creatine kinase (CK) level, 5-fold elevation of lactic dehydrogenase (LDH) levels, and 10-fold elevation of transaminases level. Inflammatory markers were negative. The immunological assay came out positive for ANA, including PM/SCL-100 and SCL-70 autoantibodies. Considering the history of a tick bite, the patient underwent serological testing for Lyme borreliosis. ELISA test was positive for IgG and also for IgM *Borrelia burgdorferi* antibodies. Infection was confirmed by western blot assay, in accordance with Centers for disease Control's (CDC) serologic diagnostic criteria [10].

Initially, myocardial necrosis enzymes (CK-MB and troponin) were elevated and NT-proBNP had slightly elevated levels. After receiving the treatment for three months, the level of these parameters normalized when the myositis reached clinical remission. The echocardiography showed a systolic dysfunction (LVEF=45%) at first evaluation with improvement after 3 months of treatment (LVEF=60%). The EKG showed diffuse T wave inversion and sinus tachycardia (Figure 3). All these findings are suggestive of cardiac involvement (myocarditis), which is a severity prognosis factor.

Electromyography of the quadriceps was performed and revealed spontaneous activity (positive sharp waves and fibrillations), low amplitude, short duration polyphasic potentials and increased recruitment of the limbs and cranial muscles. All these findings were suggestive of myopathy.

Muscle biopsy of the right thigh showed muscle fiber necrosis, internalized muscle fiber nuclei and endomysial inflammatory infiltrates (Figure 4).

Nailfold video capillaroscopy showed moderate decrease in capillary density, frequent dilated capillary loops, rare megacapillaries, very rare recent microhemorrhages, frequent ramified loops – suggestive for active scleroderma-like pattern [11] (Figure 5).

The patient underwent high-resolution computer tomography scan (HRCT) of the head-neck- chest-abdominal-pelvic areas and showed patchy ground

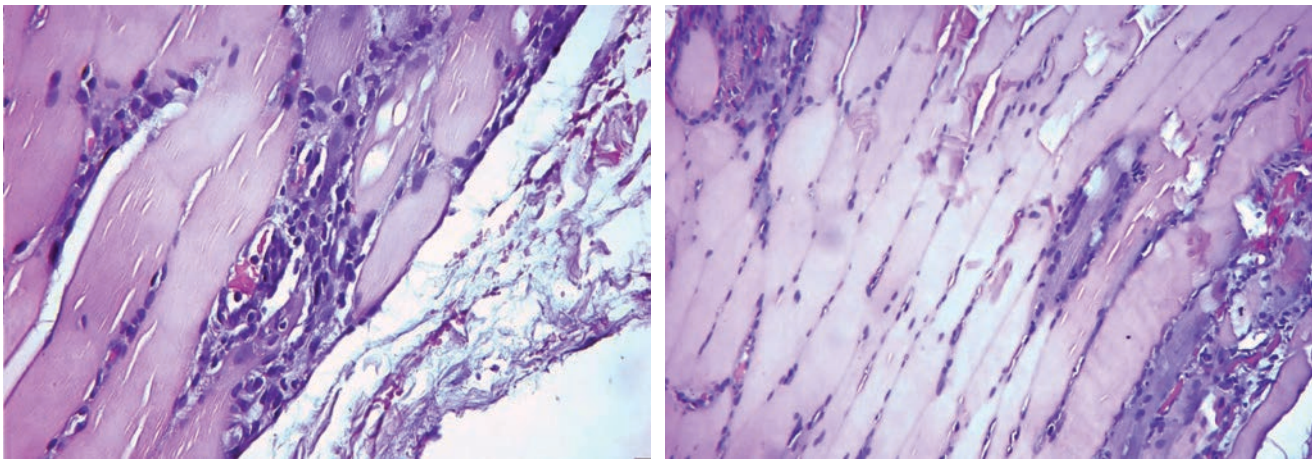

FIGURE 4 - Muscle fiber necrosis and mild infiltrates of inflammatory cells

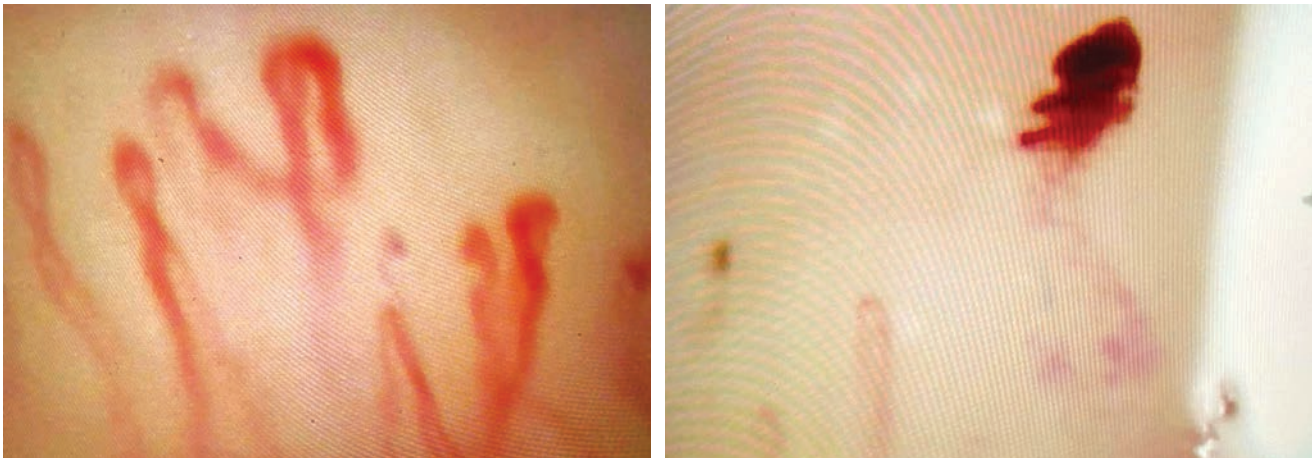

FIGURE 5 - Scleroderma-like pattern

glass opacification in the inferior lobe of the left lung that is suggestive for interstitial lung disease.

Differential diagnosis was challenging. An accurate diagnosis included ruling out a number of other possible diseases.

New onset neurological disorders were excluded by clinical and paraclinical tests, for example elevated levels of muscle enzymes, endomysial inflammatory infiltrates at muscle biopsy and electromyography suggestive of myopathy. An endocrine disorder like myxedema was ruled out by normal ranges of thyroid hormones.

Serological tests were negative for the following infectious disease: viral hepatitis, syphilis, HIV, toxoplasmosis, Epstein Barr virus.

Finally, other connective tissue diseases, such as systemic sclerosis and mixed connective tissue disease were excluded. HRCT showed patchy ground glass opacification in the inferior lobe of the left lung that is suggestive for interstitial lung disease.

Considering the life-threatening clinical features (involuntary weight loss, involvement of the respiratory and cervical muscles, the presence of dysphagia and cardiac involvement), the patient required aggressive immunosuppression treatment. Therefore, to obtain a better disease control we started pulse IV methylprednisolone therapy 1 g, intravenous immunoglobulins (IV Igs) 1.5 g per kg of body weight divided in 3 days, associated to Cyclophosphamide, 1 mg per kg of body weight per month, for the following 6 months. Between corticosteroid pulses, the patient was given prednisone, medium dose, 15 mg per day.

She also received 21 days doxycycline antibiotic treatment for *Borrelia burgdorferi* infection and trimethoprim-sulfamethoxazole for prevention of *Pneumocystis jirovecii.*

As a consequence of severe dysphagia, the patient received nasogastric tube feeding and parenteral nutrition.

After three months of treatment, the clinical features have improved remarkably, also the muscle strength and dysphagia; the CK levels rapidly decreased, reaching normal values. The patient could stand without help, she could walk, and moved from tube feeding to normal oral feeding (Figure 6).

FIGURE 6 - Muscle strength of the proximal part of the limbs recovered

DISCUSSIONS

Taking into account the history of the neurological pathology (epileptic encephalopathy and global development delay), it has been necessary to perform the differential diagnosis between a myopathy and a neurological pathology. The diagnosis of myopathy was supported by the presence of elevated levels of muscle enzymes (50-fold elevation of plasma creatine kinase (CK) level, 5-fold elevation of lactic dehydrogenase (LDH) levels), muscle biopsy (showed muscle fiber necrosis, internalized muscle fiber nuclei and mild endomysial inflammatory infiltrates) and electromyography (spontaneous activity (positive sharp waves and fibrillations), low amplitude, short duration polyphasic potentials and increased recruitment of the limbs and cranial muscles). In addition, Myasthenia gravis and Eaton Lambert syndrome were excluded due to the absence of ophthalmic muscles involvement, autonomic symptoms and acetylcholine receptor antibodies, tested multiple times.

After we concluded that the clinical and paraclinical abnormalities supported the diagnosis of myopathy, we followed up by determining the cause of the myopathic syndrome.

Levetiracetam (LEV) is an anticonvulsant commonly used for treatment of seizure disorder. One rarely reported side effect of this drug is rhabdomyolysis. In almost all of the cases included in literature rhabdomyolysis with elevation in CK levels was observed within 12-36 h of initiation of LEV. In our case LEV had been administrated for several years, so a toxic myopathy was excluded [12].

An endocrine disorder, like myxedema, was ruled out by normal ranges of thyroid hormones.

Serological tests were negative for the following infectious disease: viral hepatitis, syphilis, HIV, toxoplasmosis, Epstein Barr virus, but ELISA test was positive for IgG and also for IgM *Borrelia burgdorferi* antibodies. There are reports in literature associating *Borrelia b.* infection with polymyositis, typically occurring in the second stage of the infection. In the case of our patient, considering the presence of IgM antibodies, they are indicative of an early stage. Furthermore, the absence of erythema migrans, which is indicative of the first stage of the disease, was noted. Nevertheless, the patient was administrated a 21-day

regimen of Doxycycline, a broad-spectrum antibiotic known for its efficacy against *Borrelia b.* infections [13,15].

Clinical manifestations (proximal muscle weakness of the upper and lower extremities, involvement of cervical muscles, the presence of dysphagia) combined with CK increased levels and endomysial inflammatory infiltrates showed by muscle biopsy due to EULAR/ACR classification criteria for adult and juvenile idiopathic inflammatory myopathies were suggestive for an inflammatory myopathy [16]. The diagnosis of polymyositis is supported by the muscle biopsy (endomysial inflammatory infiltrates) and by the favorable response to treatment. Overlap myositis was deemed less likely due to the transient presence of antibodies, the lack of sufficient findings for other connective tissue diseases, such as systemic sclerosis and mixed connective tissue disease, and the endomysial inflammatory infiltrates.

Metabolic myopathies were included in the differential diagnosis of this case. Among these we mention McArdle disease (but the muscle biopsy was negative for glycogen deposits, therefore excluding this diagnosis), carnitine deficiency and carnitine palmitoyltransferase I (CPT I) deficiency.

PM can be the sign of existing cancer or may also increase the risk of the malignancy. Tumors of breast, lung and colorectal cancer are diagnosed as the three most common malignancies. Thus, the patient underwent high-resolution computed tomography scan of the head-neck-chest-abdominal-pelvic areas, to rule out a paraneoplastic cause of PM [17].

In rare cases, PM can present as a life-threatening condition due to extra-muscular involvement such as pulmonary, digestive and cardiac involvement. Even though steroids constitute the building block of treatment of this disease, in severe cases IVIg combined with an immunosuppressor should be considered in order to obtain good clinical outcomes [18]. Immunosuppressive therapies are used in addition to steroids to treat this condition; however, besides to their known adverse effects, some of them frequently failed to control the disease.

IVIg does not have a clear mechanism of action and it is considered to have a multifactorial one. IVIg acts as an immunomodulatory drug, therefore it reduces the production of autoantibodies, inhibits complement activation, neutralizes the assailant autoantibodies or autoantigens and causes cytokines suppression or blockage. Some studies recommend IVIg as first line-therapy in myositis patients along with other immunosuppressants if the patient has interstitial lung disease or dysphagia. In our case, the patient suffers of dysphagia [18]. The options of potent immunosuppressive drugs are Mycophenolate mofetil and Cyclophosphamide. Taking into account the medication options in our clinic and the fact that the patient does not want a pregnancy in the future, Cyclophosphamide was chosen. It is known that patients receiving Cyclophosphamide have an increased risk of developing an acute cardiomyopathy, but there are no reports of cyclophosphamide toxicity at less than 100 mg/kg [19]. Thus we started monthly intravenous immunoglobulins (IVIgs) 1,5 g/kg in 3 days, associated to Cyclophosphamide, 600 mg/month, and pulse IV methylprednisolone therapy 1 g/month in 4 days.

Cyclophosphamide, is an immunosuppressive agent that interferes with deoxyribonucleic acid replication and is toxic to rapidly dividing cells. It shows efficacy in clinical trials in which were included sever and refractory PM disease. Considering its side effects, it is usually reserved for treatment of severe cases of polymyositis. However, no standardized therapeutic guidelines for treatment of PM have been established. Furthermore, the presence of different disease subtypes makes the management of this condition more challenging [20,21].

Considering the severity of clinical presentation of our patient (involuntary weight loss, involvement of the respiratory and cervical muscles, the presence of dysphagia and cardiac involvement), despite the known side effects of Cyclophosphamide and intravenous immunoglobulin therapy, we decided to initiate monthly intravenous pulse therapy in order to obtain remission of the PM.

After 6 months of therapy, disease remission was achieved with a total dose of 2,4 g of Cyclophosphamide. At this point, we had to choose an immunosuppressant for the maintenance therapy of immunosuppression. Among Azathioprine (AZA), Mycophenolate mofetil (MMF) and Methotrexate (MTX), MMF was chosen because it is recommended in interstitial lung disease, being less toxic and having antifibrotic properties. Furthermore, MMF allows reduction or discontinuation of Prednisone without worsening of symptoms or objective progression of disease [22,23].

In case of relapse, Rituximab is a favorable option, as there are studies that have included patients with polymyositis and dermatomyositis who received corticosteroid therapy and at least one immunosuppressant/immunomodulator and showed a favorable response in case of relapse or treatment resistance [24].

Regarding the immune alterations induced by infection with *Borrelia b*, a small number of case reports has suggested that it may be associated with the presence of antinuclear antibodies due to molecular mimicry [25]. Similar data does not exist for the association of *Borrelia b.* infection with Scl-70 and PM-Scl-100 antibodies.

CONCLUSIONS

Adult onset polymyositis, a rare autoimmune disease, being a life-threatening condition in a few cas-

es, can be a challenge for diagnosis. Considering the complex differential diagnosis of polymyositis, multiple investigations were required to establish the diagnosis.

In our case, the patient received aggressive immunosuppressive treatment, due to the life-threatening clinical features (involuntary weight loss, involvement of the respiratory and cervical muscles, the presence of dysphagia and cardiac involvement). The serological response was prompt, and the symptoms improved progressively. At 6-months follow-up, the patient recovered almost completely on a combination of immunosuppressive and antibiotic therapy.

In conclusion the presented case report illustrates that polymyositis may be a life-threatening condition which may require aggressive immunosuppressive therapy. Our case had a good therapeutic response to Cyclophosphamide, steroid and IVIGs treatment.

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