Benefit of intravenous immunoglobulin in a patient with longstanding polymyositis/systemic sclerosis overlap syndrome

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ACTA REUMATOL PORT. 2015;40:176-178

ABSTRACT

The authors describe the case of a 49-year-old female with a progressive tetraparesis with two years of evolution, whose diagnostic study revealed a polymyositis/systemic sclerosis overlap syndrome. The patient was completely dependent and bedridden and had pulmonary, gastrointestinal, skin and bone involvement. This case intends to report and document that the use of "last-line" treatments such as intravenous immunoglobulins are effective and can be a therapy of great impact on the quality of life of the patient, even when apparently irreversible injury is established.

Keywords: Immunoglobulin; Polymyositis; Systemic sclerosis.

INTRODUCTION

The idiopathic inflammatory myopathies are rare sporadic disorders, with an annual incidence of approximately one in 100,000[1]. Polymyositis (PM) is more common in women over the age of 20 years. Patients usually have subacute symmetric proximal limb muscle weakness, and dysphagia in one third of the cases[1]. In the rare patients with a quadriparetic presentation, weakness of jaw-opening is frequently noted (71%).[1] After the onset of PM, patients have a chance of about one in four to be diagnosed with an associated connective tissue disease (CTD), such as systemic sclerosis (SSc) or lupus[2]. Depending on the classification criteria used, the frequency of myositis associated with CTD was 24 to 60% in an analysis of 100 French Canadian patients[2]. In addition to elevated antinuclear antibodies (ANA), patients with overlap syndromes (OS) may be weaker in the proximal arms than the legs mimicking the pattern seen in some muscular dystrophies[1].

Treatment is based on corticosteroids and/or others immunosuppressants regarding the clinical context, immunological markers and comorbidities. Intravenous immunoglobulin (IVIG) may be considered among treatment options in PM patients who are unresponsive to first-line immunosuppressive therapies[3].

CASE REPORT

The authors present the case of a 49-year-old caucasian female with no relevant past medical history. She had been seeking medical care for two years for progressive "paresis" of the four limbs (first the lower and then the upper). She was admitted to the hospital, in the Neurology department, on June/2012 with apparent tetraparesis. Objectively, her muscle strength was: grade 4 on shoulder elevation; 4 on fingers abduction; 3 on thumb opponency; 3 on proximal limbs movements and knee extension; 3 on foot dorsiflexion and 4 on flexion. The bicipital and brachioradialis deep tendon reflexes had an enlarged area of stimulation symmetrically. She presented also sarcopenia, dysarthria, dysphonia, dysphagia and generalized joint pain.

The workup study revealed: ESR 97 mm/h, increased transaminases (AST 120U/L, ALT 83U/L), elevated muscle enzymes (CK 2399 U/L and aldolase 81.1 U/L), ANAs >1/1000 homogeneous pattern; negative anti-Jo1, anti-Scl70, anti-centromere, anti-RNP antibodies. The electromyography showed myopathic features (decreased duration and amplitude of motor unit actions potencials with increased recruitment and some spontaneous activity) on the common extensor of the fingers and tibial anterior muscles bilaterally. She per-

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formed a biopsy of the left deltoid muscle that showed extensive foci of inflammatory infiltrate composed of mononuclear cells, located predominantly in the endomysium, dissociating the muscle fibers with occasional necrotic fibers under phagocytosis and frequent fibers in regeneration are identified. Fibers with "rimmed vacuoles" and perifascicular atrophy were not observed. The electron microscopy analysis of an muscle cut showed several small vessels with normal endothelium and the few muscle fibers found were in a early stage of necrosis with extensive areas of the sample occupied by inflammatory cells, with no abnormalities in the basal lamina of the muscle fiber, consistent with polymyositis. A skin biopsy revealed mild elastosis and fibrosis of scleroderma diffuse type. Other neurological, infectious, metabolic and drug-induced causes were excluded.

Gathering the muscle deficit and the changes found in the exams, the diagnosis of PM/SSc OS was the most probable. The patient started five pulses of methylprednisolone (1g/day), followed by oral prednisolone 80mg/day, but only with analytical parameters response (AST 35U/L, ALT 48U/L, CK 309, U/L and aldolase 16,1 U/L). She also started physical rehabilitation and speech therapy. During hospitalization, as a result of dysphagia, she developed aspiration pneumonia and type I respiratory failure. Nasogastric tube was placed for feeding and she was treated with piperacilin/tazobactam with amelioration. She was transferred to the Rheumatology department, still bedridden and dependent for daily activities. We also verified the presence of sclerodactily, facial telangiectasias and microstomia that further confirmed the previous diagnosis suspicion. As she was recovering from a serious infection but still with serious muscle involvement it was decided to start treatment with IVIG (2g/kg on a five day cycle). Surprisingly, she had not only a drastic decrease in muscle cell lysis parameters (AST 18U/L, ALT 12U/L, CK 66, U/L and aldolase 4.1 U/L), but also a fast motor recovery. Within a week the patient started walking with assistance, with progressive increase in autonomy and improvement of muscle strength (grade 4 for all previous evaluated muscles).

Throughout the study, interstitial lung involvement (ILD) with restrictive syndrome, esophageal dysmotility and osteoporosis were also diagnosed. Nailfolf capillaroscopy showed ectasias and giant capillaries with hemorrhagic foci, consistent with active pattern of SSc. Concomitant neoplasias (lung, breast, thyroid, hematologic, gynecologic and gastrointestinal) were excluded. She continued physical rehabilitation and was discharged under 10mg/week methotrexate and prednisolone 20mg/day.

A month later, she tried to eat against medical advice with consequent aspiration pneumonia and severe respiratory failure requiring invasive ventilation and hospitalization in an intensive care unit. In this context, a percutaneous gastrostomy was placed. She restarted IVIG treatment (each cycle with a total dose of 80 g), showing progressive improvement of dysarthria and dysphagia (with positive response in the swallowing test). She began walking without support, returned to her daily routine and had a significant body mass increase.

Currently, she discontinued treatment with IVIG (after one year of therapy) and maintains methotrexate 15mg/week and 5mg/day prednisolone. She is on clinical and analytical remission and began oral feeding gradually, without complications. There was no progression of ILD and recent pulmonary function tests showed only mild obstructive syndrome.

DISCUSSION

This case stands out not only by the clinical severity and disability of the patient with 2 year evolution, as by the treatment response to IVIG, which is a drug used in refractory inflammatory myopathies, but whose effectiveness has not been documented in large randomized controlled trials.

At diagnosis, myositis treatment should be initiated with high-dose corticosteroids prednisone at a dosage of 0.5 to 1 mg/kg per day[2,4,5]. Usual choices for coadjutant immunosuppression are methotrexate (MTX), azathioprine and mycophenolate mofetil. No trials have shown the superiority of one over the others[4]. If treatment fails to induce disease remission or in cases of rapidly progressive disease with severe weakness, IVIG can be administered. Regarding PM, studies have been mainly uncontrolled, but results have been encouraging, particularly in a prospective study of chronic refractory PM showing long-term improvement in 70% of 35 patients and a relapse rate of 28% in patients after stopping IVIG[5]. A distinct advantage of IVIG therapy is the ability to use it as add on therapy or in combination, even in the setting of infection, as it happened in this particular case. The improvement in strength can be seen as soon as 2 weeks after the first infusion, but the disadvantage is its con-

siderable expense[5]. As described above, our patient showed great physical and analytical improvement within a week.

On a recent review study of eleven articles, with a total of 205 patients with PM/Dermatomyositis (DM), IVIG showed: clinical improvement in 27.3% to 93.3% patients; significant improvement in scores of muscle strength and neuromuscular symptoms (P<0.018), comparing to placebo, symptomatic relief, decrease CK level, and reduced daily maintenance corticosteroid doses[6,7]; effectiveness in most patients with lung involvement and esophageal involvement; long-term efficacy of a combination treatment with corticosteroid and IVIG, including those with refractory or relapsed disease in long-term follow-up[7].

At present, no definitive guidelines are available regarding initial dose, total days of administration, and timing or dosing of subsequent administration of IVIG for DM or PM. Several studies suggested IVIG at a dose of 2g/kg body weight over a 5-day period, followed by monthly doses over 1 to 5 days for a period of 3 to 6 months[3,5,7]. It's believed that improvement tends to occur by the end of the first or second IVIG course, and that if no improvement is seen by this time, it is unlikely to be effective[3].

Poor prognostic factors in PM/DM patients include longer symptom duration, ILD, dysphagia, which our patient had, as well as older age, male gender, non-caucasian ethnicity, cardiac involvement, cancer, and serum myositis-specific antibodies (coexistence of anti-Ro52 and anti-Jo1 antibodies, presence of anti-signal recognition particle antibody, anti-155/140, and anti-CADM-140 antibodies)[1,8].

Longer duration of symptoms seems to predict non-remission of PM/DM. Thus, in a series of 77 PM/DM patients, only 9% of patients whose PM/DM was diagnosed within a period longer than 18 months between clinical symptom onset and therapy institution achieved remission; the authors suggested a possible relation to the extent of histologic irreversible muscle damage. They also found that a delay in diagnosis was a predictive parameter for mortality in PM patients. Another case series study reflected that the 10-year survival rate was significantly decreased in PM patients compared with those without esophageal involvement and dysphagia (35% vs 90%; P<0.001). Taken together, esophageal involvement and dysphagia reflect a more severe and diffuse muscle disease, resulting in a worse prognosis.8 The reasons outlined before increased our skepticism about the effectiveness of IVIG treatment in this specific patient. Fortunately, it was decided to treat her and she recovered her muscle function gradually rising from wholly dependent to being autonomous and finally regaining her ability to feed orally.

We consider important to report this case both by the clinical severity with multiple poor prognostic factors (delayed diagnosis, longstanding disease, pulmonary and esophageal involvement), but also for the effective response of IVIG, against all odds. We underline the use of IVIG reversing seemingly permanent damage, which allowed the recovery of life quality of a young patient.

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