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WHEN SHE GOT WEAKER BY THE WEEK: AN INTERESTING CASE OF IMMUNE MEDIATED MYOPATHY

Neurology

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ABSTRACT

Immune mediated necrotizing myositis (IMNM) is classified under the umbrella of immune mediated myopathies. It is an important subgroup because of the specific antibodies associated with it, and the clinical significance in terms of disease progression and treatment response which is unique for each antibody. Here, we report a case of a 50 years old female who presented with severe proximal weakness of lower limbs, myalgia and hyporeflexia. Examination also revealed flail symmetrical weakness, with generalised muscle wasting and scapular winging. Muscle tenderness was present on palpation. Her creatine kinase levels were over the roof, nearly more than 20-fold elevated. Electromyography showed myopathic changes and hence she was tested for myositis, and found to be positive for anti-SRP antibodies. She required adjuvant immunosuppression in addition to steroids and finally improved with Rituximab. The importance of a timely diagnosis of IMNM cannot be more emphasized as it bears major consequences for treatment response and progression.

KEYWORDS

Immune mediated necrotizing myositis, proximal weakness, muscle-specific antibodies, anti-SRP positive myopathy

INTRODUCTION

Immune mediated myopathies is an important group of disorders characterized by muscle weakness, elevated muscle enzymes and inflammatory infiltrates on histopathological examination of the muscle. At present, there are two classes of pathological antibodies described; the muscle specific antibodies (MSA) and the muscle associated antibodies (MAA). While the former are seen only in the presence of an inflammatory myositis, the latter may be seen in overlap syndromes with other autoimmune disorders. The presence of a muscle specific antibody is very helpful as one may discern the clinical course of the disease, possible extra-muscular manifestations and its association with malignancy. Most importantly, it provides valuable information about response to treatment and a sense of closure to both the patient as well as the physician.

Case Presentation

A 50 years old female, a home-maker by occupation, presented with chief complaints of difficulty in walking for the past 2 weeks in the form of difficulty in getting up from squatting position and difficulty in climbing stairs. Initially she used both her hands to support herself while getting up and later she required the support of one person to be pulled up. She also had severe pain over both thighs which gradually involved the arms as well. The lower limb weakness progressed within a span of 2 weeks to an extent that she was unable to walk without support. A week later she had difficulty in lifting heavy objects with her upper limbs and could not raise her arms overhead. She was also unable to turn from side to side in her bed, and could not even lift her head off the pillow. She did not have dysphagia, dysarthria or ptosis. Patient was not on any drugs prior to the onset of symptoms, statins included. There were no sensory, cerebellar or autonomic symptoms.

Figure 1- 50 years old female who presented with subacute onset proximal limb weakness

On examination, there was generalised muscle wasting, with patchy hyperpigmented lesions around neck and trunk region. There was significant wasting of proximal muscles and bilateral scapular winging was present. She had severe muscle tenderness, motor power examination revealed severe symmetrical and flail, proximal more than distal weakness, affecting lower limbs more than upper limbs, with diffuse hyporeflexia. There were no fasciculations, no hypertrophied muscles, and the sensory examination was normal. Muscle enzymes were significantly elevated, with the creatine kinase levels beyond 12,000 U/L. Her cardiac evaluation was normal, with the 2D-echocardiogram showing normal parameters. An HRCT of the chest did not show features of interstitial lung disease and an antibody profile for common overlap rheumatological syndromes also turned out to be negative, including rheumatoid arthritis, systemic lupus erythematosus (SLE), Sjogren syndrome, systemic sclerosis and mixed connective tissue disorder (MCTD). Thyroid function tests were well within range, and a thorough examination showed no evidence of Raynauds phenomenon, subcutaneous calcifications or the characteristic skin changes of dermatomyositis. Electromyography revealed multiple fibrillation potentials, positive sharp waves and myopathic motor unit action potentials (MUAPs). Based on the above features, a serum myositis panel was sent which turned out to be positive for anti-SRP (signal recognition particle) antibody. Hence, she was diagnosed with anti-SRP positive immune mediated necrotizing myositis (IMNM).

M-Scl75	NEGATIVE	Systemic sclerosis (2-3%),
JO-1	NEGATIVE	Polymyositis (25%-55%), SSc, SLE or interstitial lung fibros
SRP	STRONGLY POSITIVE 3+	Polymyositis (5%), Necrotising myopathy (anti-SRP S
PL-7	NEGATIVE	Myositis (3%-6%), Some cases overlapping with SSc
PL-12	NEGATIVE	Myositis (3%), Fibrosingalveolitis, are also frequently present

Figure 2- Serum Myositis Panel Showing Positivity For anti-SRP

Patient was initially given a course of IV methylprednisolone for a duration of 5 days and later switched over to oral steroids. One week later she was also started on adjuvant immunotherapy with mycophenolate mofetil at a dose of 500 mg twice daily. She was screened for presence of co-existing myocarditis but her cardiac biomarkers were normal. There was partial improvement of symptoms and she was discharged. However, she came back to us within a period of ten days with worsening weakness and an intercurrent UTI due to which we had to readmit her. After the treatment of her infection, we

gave her a course of Intravenous immunoglobulin (IVIG) at a dose of 2g/Kg over a period of five days and again there was only minimal improvement. The MRC power grading did not improve and as the disease was refractory to therapy, we went ahead with a fortnightly course of Rituximab injections at a dose of 1g every 15 days. The adjuvant immunosuppressive therapy was continued. Patient showed significant improvement and regained motor power of 4 in upper limbs and lower limbs and achieved independent walking. Her creatine kinase levels decreased to 1500 U/L. She was reviewed on a monthly basis and her symptoms responded well to Rituximab, with the patient being able to carry out all her daily activities of living independently thereon.

DISCUSSION

Immune mediated inflammatory myopathies are characterized by a triad of muscle weakness, elevated muscle enzymes and inflammation present on muscle biopsies. IMNM is a very important subtype of this group of disorders because the clinical features, serological profile and histopathological findings are unique to this subtype and bear a prognostic significance. IMNM may further be classified into three subtypes:

A) Anti-SRP positive IMNM
B) Anti-HMGCR (HMG Co A receptor) positive IMNM
C) Seronegative IMNM

The SRP complex is located at the surface of the endoplasmic reticulum (ER) responsible for polypeptide translocation into the ER. Both IgG1 and IgG4 autoantibodies are found against SRP. These antibodies attach to the target autoantigens located on the surface of the cell or could also penetrate into the muscle fibres. This is followed by binding and activation of the classical complement pathway. Myophagocytosis is then initiated by the macrophages and the pro-inflammatory cytokines released, lead to the beginning of muscle atrophy. Muscle regeneration usually occurs secondary to myoblast differentiation but this process is also hindered by the autoantibodies. It is also believed that the binding of autoantibodies to these target antigens initiates non-immune mechanisms such as TRIM63 mediated muscle atrophy which further adds fuel to fire.

Similarly, HMGCR is a glycoprotein whose cytoplasmic domain is attached to the membrane of the ER. A variable number of patients with anti-HMGCR positive IMNM are exposed to statins. Statins produce muscle related symptoms in about 20% of patients using them but this is mostly due to their direct toxicity. In genetically predisposed individuals, statins trigger an immune response towards HMGCR.

Overall, IMNM is more common in females with onset after 40 years of age. Seronegative IMNM is even more rare and is of importance due to its greater association with malignancy. The onset of types of IMNM is usually acute or subacute, with lower limb proximal weakness being disproportionately greater than upper limb weakness. Presenting features include myalgia and muscle weakness. Dysphagia is frequent with anti-SRP positive myopathy, which also seems to be the subtype with more severe muscle weakness. Other frequent associations of anti-SRP positive myopathy include interstitial lung disease and myocarditis. One third of all patients with IMNM may have an insidious onset slowly progressive clinical course but this is associated with obvious muscular atrophy. Also, scapular winging may be seen in IMNM.

Serum creatine kinase levels are extremely elevated (usually more than 20-30 times the normal value) and they have prognostic correlation.

Serologically positive IMNM patients do not require a muscle biopsy for diagnosis. On the other hand, seronegative patients always require a muscle biopsy for confirming the diagnosis. Around 20% of muscle fibres are found to be necrotic. The sarcolemma shows positive staining for MHC class I but MHC class II is absent. Immunohistochemistry reveals CD-56 positive fibres (indicating increased turnover) and p62 positivity within the sarcoplasm of muscle fibres (marker of autophagy). While muscle MRI can be used to quantify the degree of muscle damage, it is less useful for diagnostic purposes due to lack of specificity.

Overall, IMNM is a severe disease, especially seropositive IMNM, as muscle atrophy occurs very early during the course of the disease. Fatty replacement of muscles is common. However, the five-year survival rate of seronegative IMNM is lower than that of seropositive IMNM, mainly due to its association with malignancy.

It is a rule rather than exception that patients treated with corticosteroids require a second-line agent. Anti-SRP positive IMNM is least likely to respond to steroids. Usually, methotrexate is prescribed as a steroid sparing agent. IVIG is also preferred, especially in cases of anti-HMGCR positive IMNM. Rituximab can be used as first-line therapy in anti SRP positive myopathy but is less efficacious in anti-HMGCR positive myopathy. Monoclonal antibodies to plasma cells or components of the complement system may be the future of therapy.

The timely diagnosis of IMNM is of grave importance as muscle atrophy begins early and with greater understanding of its pathogenesis, more targeted therapies are likely to come into action. Other extra-muscular features associated with each subtype can be identified and patient may be screened accordingly. For example, it is important to rule out myocarditis in a patient with anti-SRP positive myopathy and similarly, a thorough search for underlying malignancy in seronegative IMNM is necessary as these are the factors most concerned with fatality. It is also best to inform the family that relapses are also likely. Such significant information on the prognosis and course of the disease helps in preparing the patient and his family for a spirited fight against the disease. Despite the severity of the disease and the disability it produces, the fact that it is very much treatable offers a great advantage to the physician and above all, immense hope to the patient.

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