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Internal Medicine

"THE HEAVY STEPS AND SILENT THROAT: A CASE OF IMMUNE-MEDIATED NECROTIZING MYOPATHY"

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ABSTRACT Idiopathic inflammatory myopathies are group of chronic autoimmune disorders characterized by proximal skeletal muscle weakness. One of the subtype of IIM, is immune mediated necrotizing myopathy, which is characterized by severe proximal muscle weakness, markedly elevated creatinine kinase and myofiber necrosis with minimal to no inflammatory infiltrates on muscle biopsy. Here, we describe about a case of 60-year-old male, who was not on statins, presented with bilateral lower limb swelling, symmetrical proximal muscle weakness and dysphagia. With markedly elevated CPK level, amino transaminases and Anti-SRP antibody positive in inflammatory myopathy panel, he was diagnosed with immune mediated necrotizing myopathy, who got improved only with intravenous immunoglobulins.

KEYWORDS : Anti-SRP antibody, Elevated creatinine kinase, Inflammatory myopathy, Dysphagia, Steroids, Immunoglobulins

INTRODUCTION:

Idiopathic inflammatory myopathies are group of chronic autoimmune disorders characterized by proximal skeletal muscle weakness (1).The European Neuromuscular Centre (ENMC) classifies IIM into five subgroups: Dermatomyositis (DM), anti- synthetase syndrome associated myositis (ASS), overlap myositis (OM), inclusion body myositis, and immune-mediated necrotizing myopathy (IMNM) (2). Immune-mediated necrotizing myopathy (IMNM-SRP) is a rare, severe form of idiopathic inflammatory myopathy (IIM), characterized by proximal muscle weakness, elevated creatine kinaselevels, and significant muscle necrosis (2). IMNM is further classified into three subtypes as , Anti-HMGCR antibody, Anti-SRP antibody and seronegative types. Of three, we describe here a case of anti- SRP antibody positive IMNM (2).

This case highlights the presentation of Anti-SRP antibody positive IMNM with pedal edema and dysphagia along with muscle weakness and also we aim to shed light on successful treatment strategies for IMNM with intravenous immunoglobulins in case of no improvement in muscle weakness with steroids.

CASE REPORT:

This 60-year-old male with systemic hypertension, had complaints of generalized myalgia, weakness of both lower limbs followed by difficulty in getting up from chair for the past 1 month. History of shortness of breath on exertion, history of difficulty in swallowing and nasal regurgitation for the past 15 to 20 days.

On examination, he was hemodynamically stable. On central nervous system examination, He was conscious and oriented. Speech was normal. Mild Neck weakness noted. Proximal muscle weakness over both lower limb > upper limb noted.

Blood investigation showed elevated transaminases, elevated LDH (2260) and very high CPK (11215). Urine routine showed trace proteinuria and 3-5 RBCs. Urine myoglobin was negative and Urine protein creatinine ratio was 0.92.

Since patient had complaints of shortness of breath on exertion, CT chest showed minimal sub pleural reticulations and no significant interstitial lung disease. PFT showed reduced FRC, RV, Tidal volume and low DLCO, suggestive of restrictive process.

The patient had complaints of difficulty in swallowing and nasal regurgitation, Barium swallow showed silent aspiration of contrast in larynx and trachea. FEES study was done, it showed hyperfunctioning left larynx, secretions on vocal cords and both vocal cords mobile with residue found in bilateral pyriform fossa (L>R). Swallow assessment was made with the help of a swallow therapist, found to have high risk for aspiration of liquids. Hence, Safe swallow practice was taught to attenders.

EMG showed features suggestive of a myopathic process in some of the MUPs tested – possibility of inflammatory myopathy. Vasculitis package showed ANA 3+ positive (cytoplasmic dense fine speckled), Anti-dsDNA and ANCA were negative. Inflammatory myopathy profile was strongly positive (3+) for anti-SRP antibody. With all these investigations, he was diagnosed with immune-mediated necrotizing myopathy.

He was started on IV methyl prednisolone 1 gram per day for 3 days, following that he was continued on oral prednisolone 1mg/kg/day, MMF 500mg BD and Methotrexate 10 mg/week. He was discharged and followed up as an outpatient.

After 2 weeks, he came with the same complaints of weakness over both lower limbs and dysphagia, without much improvement. He was admitted and started him on IVImmunoglobulins 30 grams per day for 4 days. Following IVIG, Repeat serum CPK showed decreasing trend (2804 U/L) and the Patient had significant improvement in weakness and dysphagia.

Summary Of Relevant Laboratory Values:

INVESTIGATIONS	VALUES	NORMAL RANGE
Hemoglobin	14.5g/dl	13-17 g/dl
White cell count	9730	4000-10,000 cubic mm
Platelet count	4,28,000	150-4,10,000 cubic mm
Urea	38 mg/dl	17-49 mg/dl
Creatinine	0.7 mg/dl	0.7-1.3 mg/dl
Sodium	135 mEq/L	136-145 mEq/L
Potassium	4.2mEq/L	3.5-5.2 mEq/L
ALT	541 U/L	< 45 U/L
ALP	55 U/L	< 116 U/L
Total bilirubin	0.8 mg/dl	0.0-1.3 mg/dl
Lactate dehydrogenase	2260 U/L	125-220 U/L
CPK	11,215 U/L	46-171 U/L
Urine myoglobin	Negative	
Urine routine	Trace protein/ 3-5 RBC	Nil
Urine spot PCR	0.92	< 0.2
ANA	3+ (Cytoplasmic dense fine speckled)	
dsDNA/ ANCA	Negative	
ANTI-SRP antibody	STRONGLY POSITIVE 3+	Negative
EMG	Features suggestive of a myopathic process in some of the MUPs tested - possibility of inflammatory myopathy	

DISCUSSION:

IMNM-SRP is one of the rare and most severe forms of IIM, characterized by profound muscle weakness, extensive necrosis, elevated CK levels, and an unpredictableresponse to immunosuppressive therapy, making its management particularly challenging (2). IMNM is found to be associated with viral infections, malignancy, connective tissue disease and toxins(1). IMNM is further classified into three subtypes based on associated autoantibodies as, Anti-HMGCR antibody, Anti- SRP antibody and seronegative (1). Both anti-SRP and anti-HMGCR myopathy tend to be most severe in younger patients (4). Anti-HMGCR and seronegative IMNM are frequently associated with malignancies (9).

Anti-HMGCR IMNM affects people around 40 to 60 years of age, with female preponderance and Statin exposure covers about 50 to 66% of these patients (9). Anti- SRP myopathy patients with very high CK levels, have more severe muscle involvement and only minority have extramuscular manifestations (1). Compared to other two subtypes, seronegative IMNM has highest association with malignancy(1).

The main clinical manifestation of IMNM is proximal limb weakness, but patients with anti-HMGCR antibody positivity progress more slowly and have less weakness than those with anti-SRP antibody positivity (3). The incidence of extra-muscular manifestations like myalgia, dysphagia, interstitial pneumonia, pericarditis, and rash was higher in patients with positive anti-SRP antibody than in those with positive anti- HMGCR antibody (3). Specifically, interstitial lung disease occurs in just 10–20% of patients with anti-SRP myopathy and in less than 5% in anti-HMGCR myopathy (4).

The diagnosis of IMNM is based on clinical manifestations, elevation of CPK, LDH and transaminases, electromyography, MRI, antibody testing and muscle biopsy (5).

In contrast to patients with other myositis, IMNM have highest CK elevations, which is correlated to disease activity (1). Muscle enzyme elevations may precede development of muscle weakness in IMNM and CK levels decrease weeks to months before muscle recovery after starting treatment (1).

In MRI, The T1WI sequence can reflect the situation of fatty infiltration, and this part of muscle damage is irreversible. The short time of inversion recovery (STIR) sequence can reflect active muscle edema associated with inflammation or muscle fibre necrosis, which can be reversed by treatment (3).

In classifying IMNM patients into its subtypes, antibody testing is a critical method (1). Anti-SRP antibody are screened by ELISA and line blot assay (1) and Anti-HMGCR antibodies are usually screened by ELISA (1).

Electromyogram may be useful early in the diagnostic workup to confirm the presence of a myopathic pattern like increased insertional activity, polyphasic, short, small MUAP with low amplitude and short duration, positive sharp waves and high frequency repetitive discharges with low level of contraction (5). These findings are nonspecific but are useful in distinguishing myopathic cause of weakness from other neuropathic disorders (5).Muscle biopsy in INMN patients show prominent necrosis and regeneration of muscle fibres along with key feature of mild or absent inflammatory infiltrates (1). Patients positive for anti-SRP and anti-HMGCR antibodies had multifocal upregulation (approximately 50%) of MHC-1 and membrane attack complex (MAC) in the presence of sarcolemmal deposition (20%-50%) of non-necrotic muscle fibers. In patients with anti-HMGCR antibodies, MAC deposition was more common in non-necrotic fibrosarcolemmas than in patients positive for anti-SRP antibodies (3).

The consensus statement issued at the ENMC workshop stated that IMNMs should be treated with both corticosteroids and immunosuppressants within 1 month of the first presentation and advised methotrexate as the initial immunosuppressant for IMNMs (3). Options available for severe disease include rituximab, IV immunoglobulin, mycophenolate mofetil and cyclophosphamide (1). Intravenous prednisolone 1 gram per dose once daily for 3 to 5 days can be used in case of severe and progressive disease (5), as in our case. In patients with resistant disease, dysphagia with risk for aspiration, intravenous immunoglobulin G is recommended (2gram per kg administered in divided doses over 2 to 5 days every 4 weeks for 3 to 6 months) (5). When both are not effective, can consider IV Rituximab (1 gram every 2 weeks for 2 doses)(5). Besides medical therapy, all patients must receive long term physiotherapy and rehabilitation (10). Thus, a multidisciplinary approach is necessary for treatment.

CONCLUSION:

This case highlights the Initial presentation of the disease with pedal edema, an uncommon presenting feature of inflammatory myopathy and Dysphagia, which need to be treated early to prevent the risk of aspiration. In conclusion, after serum CK, muscle magnetic resonance, and muscle pathological examination of IMNM to identify the disease type, myositis antibody spectrum detection should be performed to confirm the diagnosis, immunotherapy should be started as soon as possible, patients should undergo immunotherapy for a long time, and the treatment plan should be adjusted according to changes in the patient's condition during follow-up, like in our case with IVIG after steroids. Early and prompt recognition is crucial to prevent long term and irreversible damage.

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