Anti-SRP myopathy, a rare form of necrotizing myopathy in an adult Nigerian female: a case report and literature review

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Abstract

Anti-Signal Recognition Particle (SRP) myopathy is a rare form of Immune-Mediated Necrotizing Myopathy (IMNM). The IMNM is characterized by acute to sub-acute progressive severe symmetrical proximal myopathy with markedly elevated muscle enzymes. They have a variable response to steroids and immunosuppressive drugs. There are no sufficient data in African literature regarding this form of myopathy but rituximab has been used in refractory cases.We report a rare case of anti-SRP immune-mediated necrotizing myopathy in a 29-year-old Nigerian female with typical clinical, biochemical, and serologic features. A 29-year-old black African female presented with features of bilateral symmetrical severe progressive proximal muscle weakness of upper and lower limbs. She had no features of organ-specific manifestations. Drug causes of myopathy and other connective tissue diseases were excluded. Creatine kinase was markedly elevated (18824 u/L) with positive anti-SRP antibody. She received IV methylprednisolone pulses over three days, oral prednisolone at 30mg daily, and IV rituximab weekly for initial 4 weeks and 6 monthly after unresponsiveness to azathioprine. Although initially bedridden, her symptoms improved over a few weeks of treatment as she can ambulate with support. She returned to working as a chef after 2nd course of rituximab at 6 months. Anti-SRP myopathy is a rare form of necrotizing myopathy with a variable response to steroids and immunosuppressive medications.

Key words: Immune-mediated necrotizing myopathy, Anti-SRP antibody, Myofiber necrosis

Introduction

Immune-Mediated Necrotizing Myopathy (IMNM) represents a heterogeneous subtype of Idiopathic Inflammatory Myopathy (IIM) characterized by the presence of necrotic fibers, myo-regenerative bundles on muscle biopsy along with markedly elevated serum Creatine Kinase (CK) levels and severe proximal muscle weakness[1,2]. IMNM is one of the five subtypes of IIM, which include; dermatomyositis, polymyositis, antisynthetase syndrome, and inclusion body myositis[3,4]. The IMNM is a rare subtype of IIM and exact incidence and prevalence of IMNM are largely unknown. A systematic review by Meyer *et al*[5] found the prevalence and incidence of IIM to range from 1.16 to 19 cases per million per year and 2.4 to 33.8 per 100,000 people respectively. Studies done in the United States and New Zealand estimated the incidence of anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR-associated) associated IMNM to be 2 per million per year and 1.7 per million per year respectively. The incidence and prevalence of IMNM were not stated in the aforementioned studies[6,7]. However, a study done in Olmsted County Minnesota concluded that IMNM is a rare disease and it has a prevalence of one-tenth that of inclusion body myositis[8].

There are seropositive and seronegative forms of IMNM. The seropositive form are associated; Anti-Signal Recognition Particle (anti-SRP) and anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase (anti-HMGCR) antibodies[2,9]. Anti-SRP autoantibodies are myositis-specific antibodies[1,10] which act against SRP, a ribonuclear protein particle that modulates protein translocation across the membrane during protein synthesis in the endoplasmic reticulum[11,12]. Anti-SRP myopathy was recognized as a distinct form based on clinical features and histopathology features[13]. Patients with anti-SRP positive antibodies typically manifest with severe progressive myopathy, markedly elevated serum creatine kinase levels, and myofiber necrosis on muscle biopsy with or without muscle inflammation[11-13]. Moreover, they have a poor response to glucocorticoids and immunosuppressive therapies[14]. Refractory anti-SRP myopathy has been

treated with combination therapy- prednisone, plasma exchange, and repeated courses of rituximab[15].

An extensive search of Nigerian and African English medical literature showed a single case report of myositis with a combination of anti-Mi-2 and anti-SRP[16]. Therefore, we report a case of anti-SRP positive myopathy in a 29-year-old Nigerian female with typical clinical, biochemical, and serologic features.

Case report

A 29-year-old female patient presented in the Rheumatology clinic in April 2021 with complaints of rapidly progressive proximal muscle weakness in both upper and lower limbs. The weakness was characterized by difficulty raising her arms and getting up from a sitting position. The weakness in the lower limbs progressed to difficulty in walking. There was no history suggestive of other myopathies, internal organ manifestations and overlap myositis.

Her physical examination findings revealed severely weak proximal and distal muscle groups of the upper limbs and proximal muscle groups of the lower limbs (power of 2/5). Atrophy of the proximal muscle groups of both upper and lower limbs was noted. There were no significant abnormalities in other aspects of neurological and systemic examinations.

The laboratory studies revealed haemoglobin of 13.0g/dl (12-16), total leucocyte count of 3.8×10^9/L (4-11.0×10), thrombocytes of 199×10^9/L ($150-450\times10^9$), erythrocyte sedimentation rate of 30mm/hour (0-20).

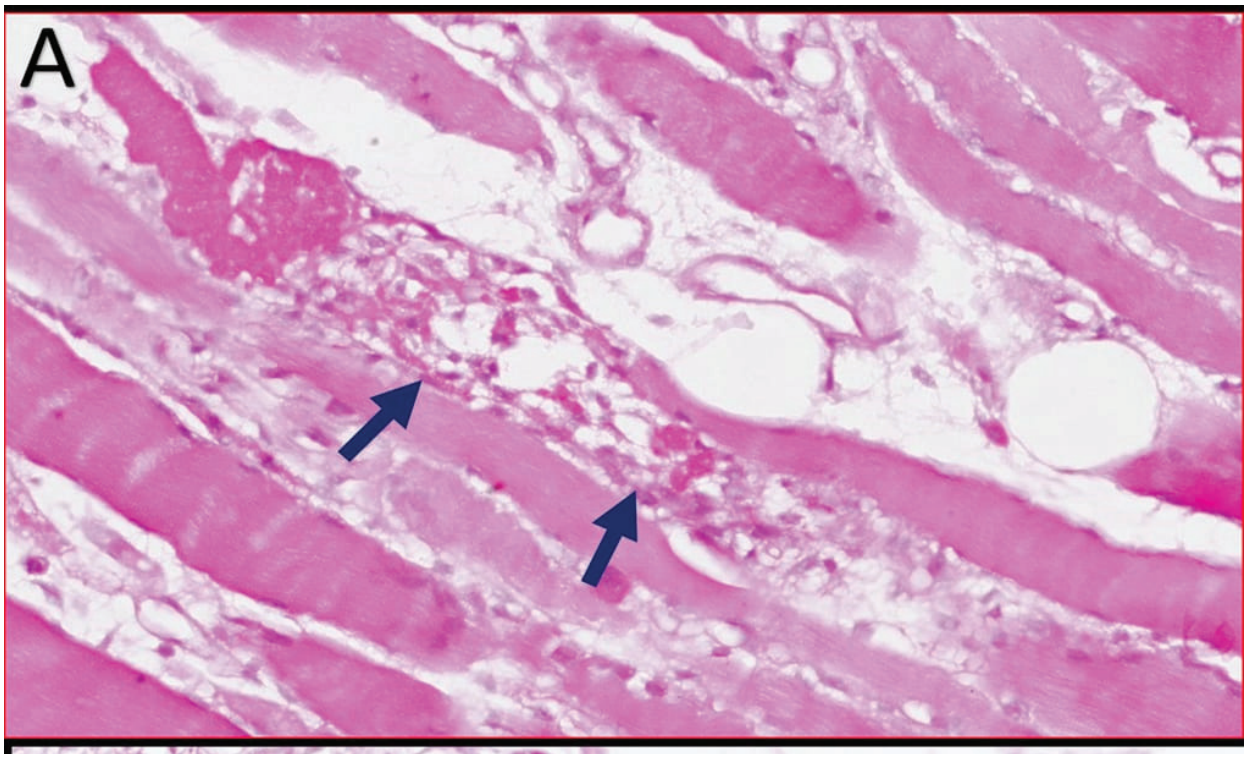
Result of renal function was normal. Muscle enzymes were elevated and these include aspartate aminotransferase (AST);467.1U/L (10-42), alanine aminotransferase (ALT); 288.9U/L (10-40), lactate dehydrogenase (LDH); 2007U/L (140-280) and creatine Kinase (CK) 18824U/L (30-135).

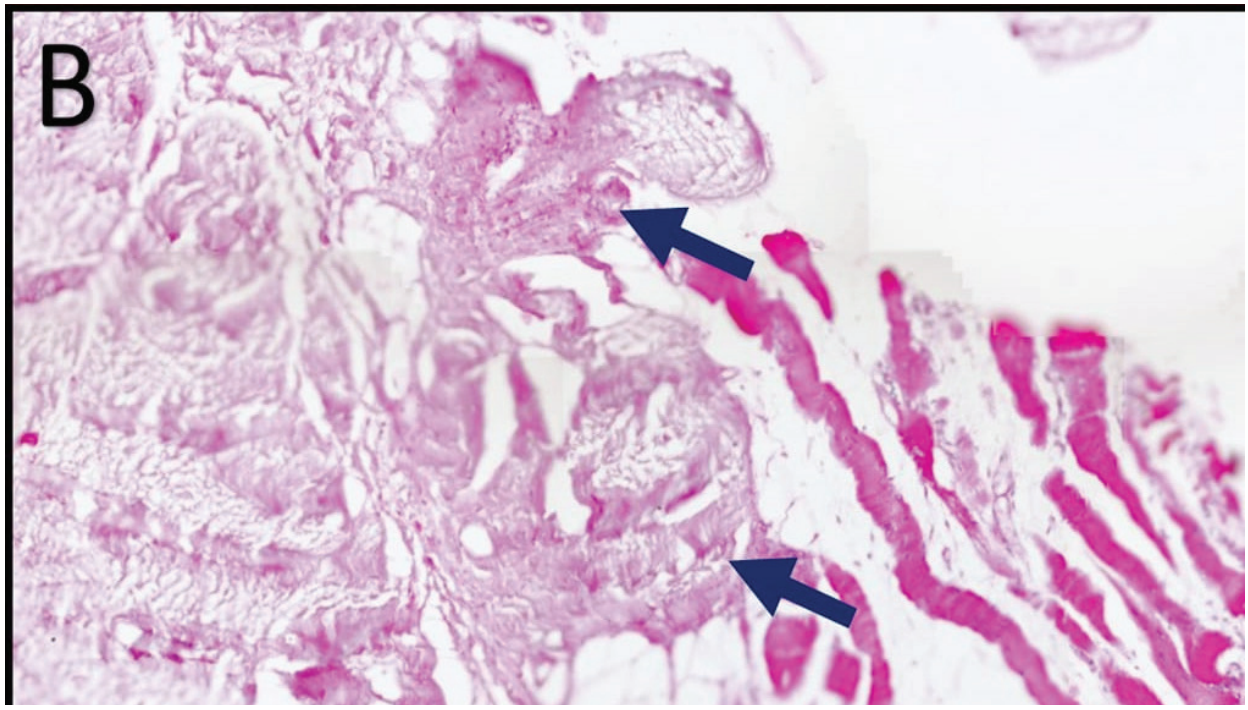
Urinalysis was normal, and screening for hepatitis B&C viruses and HIV were all negative. Electrocardiogram was normal, echocardiography revealed findings in keeping with hypertensive heart disease. Chest computed tomography scan was negative for malignancy and interstitial lung disease.

Antinuclear antibody was negative while myositis panel showed isolated positive anti-SRP antibody. Muscle biopsy revealed multiple foci of necrobiosis, and myofiber regeneration with mononuclear cell infiltrates including lymphocytes, plasma cells, and macrophages. A diagnosis of anti-SRP myopathy was made based on European Neuromuscular Centre (ENMC) criteria. Pulse therapy with intravenous methylprednisolone 1000mg for three consecutive days was administered and subsequently followed by oral prednisolone 60mg/day and azathioprine 100mg /day. She had 500mg of intravenous rituximab weekly for 4 weeks due to none improvement in her symptoms while on azathioprine. Three months later, CK levels had dropped to 635U/L, AST to 52.7U/L, and ALT to 61.5U/L with the concurrent subjective and objective improvement in her muscle weakness as she could walk without support.Oral prednisolone was tapered to 10mg over 4 weeks and continued with six monthly intravenous rituximab 500mg administered weekly for 4 weeks. The treatment was well tolerated and she returned to her job as a chef after second course of rituximab treatment.

IMNM is a rare disease with distinct clinical and histopathologic findings. The progression of muscle

Figure 1: Photomicrograph showing infiltration of the muscle by mononuclear chronic inflammatory cells including lymphocytes, plasma cells, and a few macrophages (A). There are areas of necrobiosis and myofibre regeneration (B)





weakness was rapid and severe thereby affecting independent ambulation. Refractory variant may respond to repeated rituximab administration.

Discussion

Immune-mediated necrotizing inflammatory myopathy is a rare subtype of idiopathic inflammatory myopathies characterized by acute to subacute symmetrical and severe proximal muscle weakness, elevated creatine kinase and the histological evidence of myofiber necrosis and regeneration with little or no inflammatory infiltrates[2,9]. It was first identified in 2004 and included in the new classification for IIMs[17]. In addition to traditional Polymyositis (PM), Dermatomyositis (DM), and Inclusion Body Myositis (IBM) subtypes, overlap myositis and IMNM were the newly introduced subtypes. The other variants are juvenile DM, cancer-associated myositis, and clinically amyopathic DM[18].

The IMNM is characterized by the presence of anti-Signal Recognition Particle (SRP) or anti-3-hydroxy-3-methylglutarylcoenzyme-a reductase (HMGCR) antibodies. The three subtypes of IMNM are anti-SRP positive IMNM, anti-HMGCR positive IMNM, and autoantibody (seronegative) negative IMNM[2,9,19]. Moreover, other variants of IMNM have been identified. These include cancer-associated IMNM, connective tissue disease-associated IMNM, statin-associated IMNM, and immune checkpoint inhibitors-induced IMNM[20]. The anti-HMGCR positive subtype is commonly found in statin users and together with seronegative subtypes are associated with malignancy[6]. The anti-SRP positive IMNM subtype has more frequency of extra-muscular manifestations with no risk of malignancy compared with the other two subtypes[21,22]. However, our patient does not have extra-muscular features.

The IMNM constitutes about 10% of IIMs[23]. The worldwide prevalence and incidence could not be determined due to its rarity[18]. Although IIMs are rare in native Africans, this is more so for IMNM. In a recent hospital-based study done in South Africa by Chinniah *et al*[24], IMNM and associated autoantibodies were not observed in 104 cases of IIMs. Similarly, a systematic review article on the epidemiology of IIM in Africa which included 39 studies and 683 cases did not identify any case of IMNM in African black despite documenting prevalence estimates of 11.49/100,000 for IIM[18]. To the best of our knowledge, this is the first true description of Anti-SRP positive myositis in black Africa according to the new criteria. The paucity of data may be attributable to low rate of muscle biopsy and lack of myositis antibody testing in most African countries. The use of Bohan and Peter's criteria for the classification of IIM subtypes in previous studies may lead to the misidentification of the IMNM subtype.

According to the 2017 European Neuromuscular Centre (ENMC) criteria for IMNM, the presence of proximal muscle weakness and elevated CK is enough to diagnose IMNM in those with positive Anti-SRP or anti-HMGCR[17]. Our patient fulfilled these criteria. She had subacute onset of rapidly progressive severe proximal muscle weakness within 3 weeks. However, there was absence of extra-muscular manifestations that are frequently observed in the Anti-SRP subtype. The two autoantibodies in IMNM are pathogenic as they induced myofiber necrosis through complement activation. Furthermore, the level of Anti-SRP was observed to correlate with CK level and muscle necrosis. While the titre of anti-SRP was not reported in our patient, the CK level was more than 100 times the upper limit of normal.

Despite the presence of mononuclear cell infiltration in addition to multiple foci of myofiber necrobiosis and

regeneration reported in muscle biopsy findings of our patient, this is not required to confirm the diagnosis of the anti-SRP subtype. The biopsy findings have been reported to be non-specific for IMNM as biopsy features may be seen in other myositis subtypes. Nonetheless, muscle biopsy is mandatory for the diagnosis of the seronegative IMNM subtype. The Magnetic Resonance Imaging (MRI) is not required for diagnosis but is useful in monitoring disease activity. The treatment of IMNM should not be delayed as it has the worst prognosis among the myositis subtypes. It was reported that about 50% of patients with the seropositive subtype continue to experience muscle weakness after two years of therapy. As recommended by the ENMC, our patient had a rituximab infusion after failing initial treatment with a high-dose steroid and azathioprine. There was a dramatic improvement in muscle power and a significant drop in CK months after the first course of rituximab therapy.

Conclusion

The IMNM is a rare condition and a high index of suspicion is required to promptly diagnose a suspected case. A patient presenting with subacute onset of rapidly progressive proximal muscle weakness in the presence of unusually elevated CK should raise diagnostic consideration for IMNM. The widespread availability and affordability of myositis antibody testing in sub-Saharan Africa may aid the diagnosis of seropositive IMNM and other myositis subtypes.

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