CASE REPORT

Necrotizing Autoimmune Myopathy: A Case Series

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ABSTRACT

Necrotizing autoimmune myopathy (NAM) is considered a new subgroup of a rare autoimmune idiopathic inflammatory myopathies. Classically, NAM presented with sub-acute onset of proximal muscle loss of power with raised creatinine kinase and characteristic muscle biopsy showing muscle necrosis and regeneration with little inflammation. Statin use, connective tissue diseases, malignancy and HIV infection are the identified risk factors for NAM. The autoantibodies expected to be presented in NAM are anti-signal recognition particle (SRP) and anti-hydroxymethylglutaryl-coenzyme A reductase (anti-HMGCR) antibodies. In this article, we present three cases of NAM with different risk factors and autoantibodies which we believe to have impact on the clinical course and outcome of our patients

Keywords: Idiopathic inflammatory myopathies, Necrotizing autoimmune myopathy, Antibodies

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INTRODUCTION

"Necrotizing autoimmune myopathy (NAM) is a rare subgroup of idiopathic inflammatory myopathies (IIM)" (1 p. 337). It was first proposed to be classified under the subgroup of IIM in 2003 by the European Neuromuscular working group (1). Since its introduction, several case reports and series have been published resulting in an increased awareness and importance of NAM diagnosis. Like the other subgroups of IIM, NAM is characterised clinically by gradual proximal muscle weakness frequently accompanied by high serum creatinine kinase (CK) (2). In contrast to polymyositis or dermatomyositis, muscle biopsy of NAM typically showed regenerating fibers, necrosis, and little to no inflammatory changes. We report three cases of NAM in Putrajaya Hospital, Putrajaya.

CASE SERIES

Case 1

A 55-years old female with underlying dyslipidemia presented with generalized body weakness for one month. The weakness has caused her to fall twice prior to presentation. After the second fall, she became bedbound with weakness of the upper and lower limbs, dysphagia and dysarthria. Physical examination revealed symmetrical upper and lower limbs weakness (power 3/5) with intact reflexes and sensation. There was tenderness in the region of L3. CT scan of the spine showed compression fracture at C5 with multi-level degenerative changes at the cervical spine. Further history revealed a recent dose increment of simvastatin from 20mg to 40mg daily a month prior to the fall. Laboratory investigation revealed an elevation of serum CK (7229 IU/L), alanine transaminase (ALT) of 363IU/L and aspartate transaminase (AST) of 594IU/L. Renal profile, serum calcium and phosphate were normal. Urine analysis was nil for blood and myoglobin was negative. She was treated as statin-induced myopathy statin was stopped. Although CK improved down to 4135 IU/L, there was no improvement of muscle power and patient developed significant dysphagia requiring nasogastric tube feeding. Muscle biopsy showed muscle fiber necrosis with clusters of small round regenerating fibers (Fig. 1). There was also increased macrophages reaction in association with necrotic fibers (Fig. 2) consistent with NAM. Anti-signal recognition particle (SRP) was positive but negative for other myositis-specific antibodies (MSA) and anti-nuclear antibodies (ANA). The patient was pulsed with intravenous methylprednisolone 500mg daily and subsequently given oral prednisolone 0.5mg per kg and azathioprine 50mg daily. She had some improvement in her muscle power and was discharged from hospital.

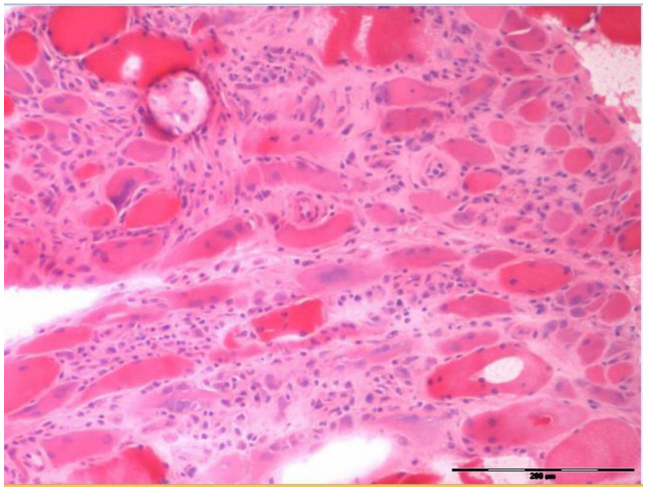

Figure 1: Muscle biopsy. Muscle biopsy showed the presence of muscle fiber necrosis and a cluster of small round regenerating fibers.

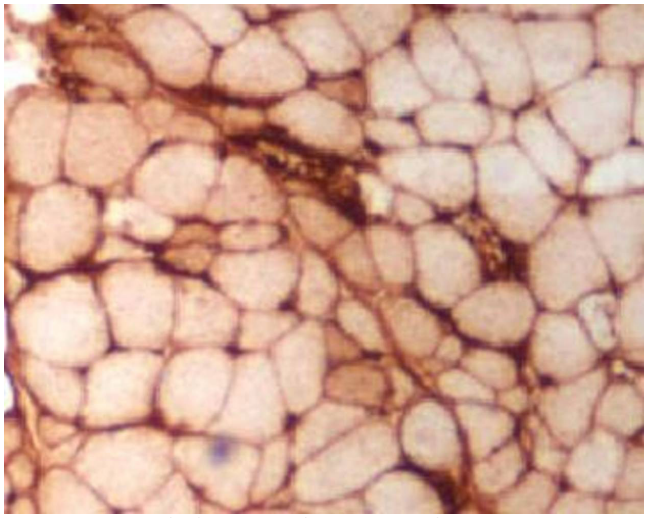

Figure 2: Muscle biopsy with necrotic fibers. Muscle biopsy showed increased macrophages reaction in association with necrotic fibers.

Case 2

A 35-years old male with no previous medical illness presented with proximal lower limb weakness for one month. He denied history of fever or symptoms of infection. There was no history of recent medication intake or supplements. Physical examination revealed symmetrical proximal lower limb weakness with hip power of 4/5. Other systemic examination was unremarkable. Laboratory investigations showed CK of 70603 IU/L with normal ALT and AST, full blood count and renal profile. ANA test was negative. Electromyography (EMG) and nerve conduction study (NCS) were normal. There was not much improvement in serum CK despite adequate hydration and his symptoms persisted. Magnetic resonance imaging (MRI) of bilateral thighs showed oedematous muscle consistent with myositis. Subsequent muscle biopsy showed necrosis and regenerating muscle strands consistent with NAM. MSA was sent and was positive for anti-hydroxymethylglutaryl-coenzyme A reductase antibody (anti-HMGCR). He was diagnosed with idiopathic inflammatory NAM and started on prednisolone 1mg per kg with azathioprine. His muscle weakness improved. However, three month after treatment he developed nasopharyngeal swelling and oral thrush. He was referred to the otorhinolaryngology team for biopsy of the nasopharyngeal mass and results showed chronic inflammation. Human immunodeficiency virus (HIV) result was positive and CD4 count was 218. He was referred to the infectious disease team for further treatment of his HIV infection.

Case 3

A 56-years old Indian lady presented with six months history of gradual onset of bilateral proximal muscle pain and weakness in 2006. Her CK was > 12000 IU/L with positive ANA 1:40. Her EMG showed increased recruitment pattern in the proximal muscle and spontaneous activity in the biceps; consistent with inflammatory myositis. Her muscle biopsy was consistent polymyositis. She responding partially with intravenous immunoglobulin, intravenous cyclophosphamide, and mycophenolate mofetil. A repeat muscle biopsy in 2010 revealed a muscular dystrophy however, gene analysis showed no deletion or duplication in the dystrophin gene.

In 2015, a trial of Rituximab commenced with partial clinical response (improving CK with no weakness improvement). MRI showed generalized muscle atrophy of both thighs with patchy T2 hyperintensities involving right sartorius, right gracilis and left gracilis muscle (Fig. 3). Her muscle biopsy in 2006 was reviewed again and it was consistent with NAM. MSA was sent and her anti-HMGCR Ab was positive. She was started on combination therapy of methotrexate and azathioprine. Since then, her CK normalized to 142 IU/L with some improvement in her muscle weakness. Full return of muscle power was not expected as she had some degree of muscle atrophy.

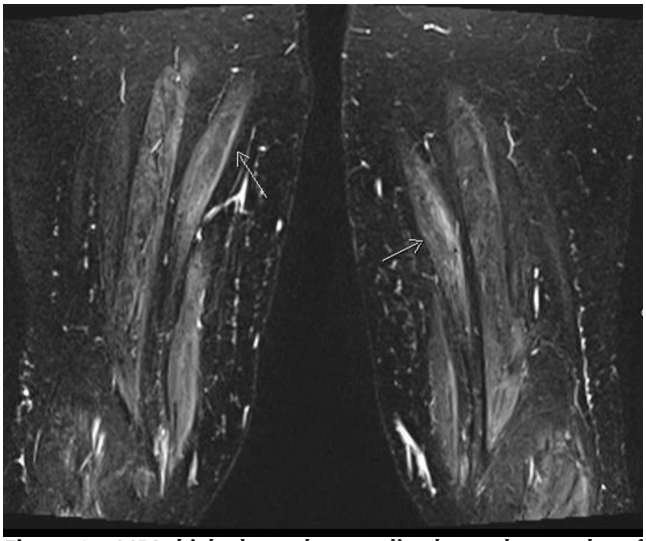

Figure 3: MRI thigh showed generalized muscle atrophy of both thighs. The thighs are with patchy T2 hyperintensities involving right sartorius, right gracilis and left gracilis muscle consistent with active myositis.

DISCUSSION

Similar to other published data of NAM, our patients presented with progressive muscle weakness with markedly elevated CK ranging from 7000 to 70000IU/L. NAM can be idiopathic in about 50% of cases (3); other known causes were statin exposure, malignancy, connective tissue disorders and human immunodeficiency virus infection. Statin use and HIV-related infection were found to be the risk factor in two out of our three cases.

Statin exposure, particularly atorvastatin and simvastatin, was found to be the most identifiable risk factor for developing NAM. In our patient (case 1), the onset of NAM was related to the dose increment of simvastatin. Our patient had profound dysphagia. Dysphagia has been described in NAM, along with other symptoms such Raynaud's phenomenon and arthralgia which absent in our cases. Stain-associated myopathy are expected to recover completely in weeks or months after withdrawal of statins. There was no improvement of muscle weakness in our patient despite a drop in the serum CK level.

HIV-related NAM is relatively rare and in the largest case series of HIV related myositis by Johnson et al, the symptoms of proximal muscle weakness can be mild with normal EMG like in our patient (case 2) and the severity of the weakness was not correlated with CK level (4). Myositis in HIV patients can also occur at any stages of the infection and there was no association found with the CD4 or CD8 lymphocytes counts.

Anti-HMGCR and anti-SRP antibodies are the two most important serologic indicators of NAM and these antibodies were positive in our cases. Anti HMGCR is more specific for NAM whereas anti-SRP has been reported to be associated with other autoimmune condition. Presences of anti-SRP antibodies in patients with NAM are linked with rapid and severe muscle power loss with dysphagia has also been reported in 30-69% of cases.

The severity of muscle weakness varies in HMGCR antibody patient and the high level of CK was not found to be corresponded to the degree of muscle weakness. Interestingly, Werner et al. found the correlation between titers of the anti-HMGCR antibodies and muscle strength among HMGCR antibody related NAM. Whether this explained the difference of the severity of the weakness in our HMGCR antibody patient's needs further study.

Case 3 illustrates the delay in diagnosis of NAM due to non-typical pathologic findings on muscle biopsy mimicking muscular atrophy. Carvalho et.al had described a case with past history of breast carcinoma and statin prescription, presented with rapidly increasing lower limbs weakness with high CK count, and dystrophic muscle histology (5). Muscular dystrophies were ruled out through gene testing, and anti-3-hydroxy-3-methylglutaryl coenzyme A reductase was positive; similar to our case.

To date, there is no guideline to the specific choice of immunosuppression for the treatment of NAM. However, most case studies of NAM reported were refractory to corticosteroid alone and need at least two immunotherapeutic agents. Early recognition of anti-SRP and anti-HMGCR myopathies is imperative, as timely immunosuppressants treatment often resulting in strength restoration.

CONCLUSION

These 3 case reports highlight the importance of recognizing risk factors and associated autoantibodies namely anti-SRP and anti-HMGCR related NAM in which it predicts the clinical course, aggressiveness of treatment, and outcome of the disease.

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