Case Report

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Necrotizing autoimmune myopathy: an emerging entity in the spectrum of inflammatory myopathies

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Background: Necrotizing autoimmune myopathy is a relatively newly recognized rare form of idiopathic inflammatory myopathy. It presents clinically with symmetrical proximal muscle pain and weakness, associated with a markedly elevated Creatine kinase level. These myopathies are usually immune mediated with a good response to immunotherapy.

Case presentation: We present a case of a 32 year old man of Asian descent, having a 6 months history of symmetrical proximal muscle weakness. Patient underwent extensive workup and was diagnosed with Necrotizing autoimmune myopathy.

Conclusion: The disease process of Necrotizing autoimmune myopathy is still not completely understood. However, a delay in the diagnosis may lead to potential complications as the disease progresses rapidly.

Keywords: necrotizing autoimmune myopathy • signal recognition particle • hydroxy methyl glutaryl Co A reductase • creatine kinase • intravenous immunoglobulin • interleukin-1 • idiopathic inflammatory myositis • interestitial lung disease • mixed connective tissue disease

Introduction

Idiopathic inflammatory myopathies are a group of chronic, autoimmune conditions affecting primarily the proximal muscles. These are identified by their clinical presentation consisting of muscular and extra muscular manifestations. Necrotizing autoimmune myopathy presents in adults with progressive proximal muscle weakness without the appearance of a rash [1]. We discuss a case of an elderly male with similar complaints, being diagnosed as a case of Necrotizing autoimmune myopathy.

Case presentation

A previously healthy 52 year old male patient presented in the rheumatology clinic with complaint of progressive weakness in upper and lower limbs for last 6 months. Weakness was characterized by difficulty standing up from sitting position, combing hair and changing clothes. Patient also complained of mild pain in multiple joints including the Proximal Interphalangeal and Metacarpo phalangeal joints of hands, shoulder joints and knee joints.

However, there was no history of dysphagia, dyspnea, skin rashes, oral ulcers, photosensitivity, and hair fall or weight loss.

Our patient was not taking any myotoxic drugs or Statins. Family history for connective tissue disorders was negative.

Laboratory investigations revealed an ESR of 65 mm/hr. with markedly elevated serum CK levels, 4418 units/L (normal range 26-192).

Till now the diagnosis seemed obvious and patient was suspected as a case of Polymyositis but on further testing ANA turned out to be positive with negative Anti-Jo-1 Antibody. At this point, we decided to do a few more investigations and in the mean while muscle biopsy was being planned. Electromyography was abnormal showing mild active degenerative upper and lower limb muscles with myopathic unit. SRP-IgG (Anti Signal recognition particle) tested positive while HMGCoAR-IgG antibodies were found to be negative. Incisional biopsy from Quadriceps muscle showed the presence of scattered necrotic myofibres with no inflammatory infiltrates.

On the basis of clinical presentation and laboratory evidence, a diagnosis of Necrotizing Autoimmune Myopathy was made.

The patient was initially started on Tab. Prednisolone 1 mg/kg/day. However, the

patient's weakness was refractory to steroid monotherapy, with CK level of 3553 U/L at 2 months of beginning the treatment. Immunosuppressive therapy was escalated to Tab. Azathioprine 0.80 mg/kg/day, 6 months after which he had a steady functional recovery and improved muscle strength. Calcium and vitamin D supplements were given as prophylaxis against steroid induced osteoporosis along with cap, Omeprazole to avoid gastric irritation. Regular blood CP and LFTs were advised to monitor azathioprine toxicity. Repeat CK was 2100 (6 months after commencing azathioprine). Steroids were tapered off gradually in a period of four weeks. The patient had improved clinically, remarkably. His last CK was found to be 150 U/L, and is presently on Azathioprine 0.5 mg/kg twice daily with regular monthly follow ups.

Discussion

The autoimmune side of NAM is evident by its association with autoantibodies directed against signal recognition particle and 3-Hydroxy-3-methyl glutaryl- co enzyme a reductase in majority of patients [2].

Majority of young patients suffering from NAM are seen to have SRP antibodies. HMGCR is pharmacologic target of the Statin drugs. Therefore, these autoantibodies are found in patients exposed to Statin medication [3]. Improvement occurs in majority of patients upon stoppage of the offending agent. In a few cases, it persists even after discontinuation of the drug. Such cases require immunosuppression therapy [4].

NAM associated with statin exposure is further discussed in the later sections.

Other than use of Statin medication, NAM can also occur on a background of neoplasms and connective tissue diseases and its association with different malignancies have been well established [5].

A study that took 63 patients who were already diagnosed with NAM, demonstrated that out of them, 22 were receiving a Statin medication specifically atorvastatin and simvastatin, 6 were suffering from cancer that included gastrointestinal adenocarcinomas (2 colonic 1 esophageal), lung adenocarcinoma, ovarian adenocarcinoma, and thymoma. 3 had a rare association with CTD, out of them 2 had scleroderma while the other was suffering from Sjogren syndrome. Rest of the 32 did not have any obvious causative factor and were termed idiopathic [6].

Regarding clinical presentation, proximal muscle weakness has been identified as the chief symptom of the disease [7]. Additional symptoms include distal and lower extremity weakness, with or without dysphagia and dyspnea [6]. Respiratory muscle involvement can lead to severe weakness of the affected muscles leading to respiratory failure in some patients requiring intubation [5].

A recently published case report shows that immune mediated necrotizing myopathies can present initially with symptoms of neck swelling and dysphagia. Prior to this report, no case has been published with initial head and neck involvement in patients suffering from NAM [8].

The diagnosis of NAM requires clinical, electrophysiological and pathologic evidence. The median CK value is several folds higher than normal. Presence of SRP (IgG) or HMGCR (IgG) is essential. Electrophysiology should show characteristic findings of myopathy recorded by EMG. The gold standard for the diagnosis remains muscle biopsy that reveals necrotic myofibres with little or no inflammatory infiltrate [6]. NAM with the presence of Anti-HMGCR is usually related to statin use. The presence of either of these antibodies predicts a response to immunotherapy [9].

A study conducted by Yves Troy et al., named NAM as a disease with a pure Polymyositis phenotype. Out of 17 patients with a clinical picture of polymyositis, 14 had NAM. Out of these 14, twelve of them were suspected of Statin induced NAM because of their previous exposure to Atorvastatin. All these 12 patients had antibodies to 3-Hydroxy-methyl glutaryl Coenzyme-A reductase, and no antibodies to SRP. The same study identified 3 stages of myopathy. Stage1 includes isolated elevation of serum CK, stage 2 includes serum CK elevation with normal muscle strength and abnormal EMG finding, stage 3 includes elevation of serum CK, proximal muscle weakness and abnormal EMG [10]. Subject in our study was identified as stage 3 candidate according to these stages.

Along with NAM, the spectrum of inflammatory myopathies includes Polymyositis, Dermatomyositis and Inclusion body myositis [11]. The Table 1 below compares the primary key features of each of them that may help reach a successful diagnosis.

Table 1. Characteristic features of different types of Autoimmune Inflammatory Myopathies

Characteristic	Polymyositis	Dermatomyositis	Inclusion body myositis	Necrotizing autoimmune myopathy
Clinical Features	Proximal muscle weakness	Proximal muscle weakness, Heliotrope rash, Gottron's papule	Proximal and distal muscle weakness, involvement of finger and wrist flexors & knee extensors	Proximal muscle weakness, infrequent dyspnea and dysphagia
Lab Investigations	Raised serum CK, Anti –Jo-1 Antibody	Raised serum CK, Anti-Mi-2 Antibody	Normal or mildly raised serum CK	Raised serum CK, Anti SRP Antibody, HMGCoAR Antibody
Biopsy findings	Endomysial inflammatory infiltrate with muscle fiber necrosis	Perifascicular, perimysial or perivascular inflammatory infiltrate, perifascicular necrosis	Single or multiple ringed vacuoles with inflammatory infiltrates	Necrotic muscle fibers with little or no inflammatory infiltrate
Associated conditions	ILD, MCTD	Lung CA, ILD, Vasculitis	Scleroderma, MCTD	Malignancy, MCTD
Treatment options	Corticosteroids, Azathioprine, Methotrexate, cyclophosphamide, Rituximab	Corticosteroids, Azathioprine, Methotrexate, cyclophosphamide, Rituximab	No proven therapy, steroids and immunosuppression show poor response	Corticosteroids, Azathioprine, Methotrexate, IVIG, cyclophosphamide, Rituximab

Treatment of NAM includes corticosteroids, oral steroid sparing immunosuppressant (methotrexate, azathioprine, mycophenolate mofetil) and IVIG [5]. Prednisone monotherapy is usually insufficient for the control of disease, as evident in our patient. There is a high risk of relapse during immunosuppressant taper or discontinuation. Many patients may require multiple immunosuppressive agents [6]. Aggressive treatment is reserved for refractory a case which includes intravenous methylprednisolone, IVIG, rituximab, cyclophosphamide and cyclosporine. IVIG may be used as an alternative to immunosuppressive agents for people who may develop toxicity against it or are unable to tolerate them [1]. Another emerging drug in the treatment of idiopathic inflammatory myopathy is Anakinra, a recombinant humanized IL-1 receptor antagonist, as there is overexpression of IL-1 in muscle tissue of inflammatory myopathies. A clinical trial revealed that out of 15 patients with refractory myositis who were treated with Anakinra, 7 of them showed a positive clinical response over a period of 12 months. The efficacy of this drug in the treatment of IIM is still under consideration and needs large scale randomized trials [12].

Conclusion

NAM is a severe immune mediated myopathy that has a variety of clinical presentations. Early diagnosis and prompt immunosuppressive therapy remains the gold standard for optimal prognosis and better clinical outcomes. The patient however needs to be followed up for a longer period of time.

Consent

Written informed consent was obtained from the patient for the publication of this case report.

Competing interests

The authors declare that they have no competing interests.

References

1. Malik A, Hayat G, Kalia JS *et al.* Idiopathic inflammatorymyopathies: Clinical approach and management. *Front. Neurol.* 7, 64 (2016).
2. Bergua C, Chiavelli H, Simon JP *et al.* Immune mediated necrotizing myopathy. *Z. Rheumatol.* 75, 151 (2016).
3. Mohassel P, Mammen AL. Statin associated autoimmune myopathy and HMGCR autoantibodies. *Muscle. Nerve.* 48(4), 477–83. (2013).
4. Needham M, Fabian V, Knezevic W *et al.* Progressive myopathy with upregulation of MHC-1 associated with Statin therapy. *Neuromuscular disorders.* 17(2) (2007).
5. Kassardijan C, Milone M. Necrotizing autoimmune myopathy. *Springer.* 3(4) 267–274 (2016).
6. Kassardijan C, Lennon VA, Nora B *et al.* Clinical features & treatment outcomes of Necrotizing autoimmune myopathy. *JAMA neurology.* 72(9) 996–1003 (2015).
7. Ashton C. Necrotizing autoimmune myopathy. *ACNR.* 17(1) (2016).
8. Ngo LQ, Wu AG, Mathew A *et al.* A case report of Necrotizing myositis presenting as dysphagia and neck swelling. *BMC. Ear. Nose. Throat. Disord.* 16(7) (2016).
9. Meriggioli MN. The clinical spectrum of Necrotizing Autoimmune Myopathy. A mixed bag with blurred line. *JAMA Neurol.* 72(9) (2015).
10. Troyanov Y *et al.* Atorvastatin induced necrotizing autoimmune myositis, an emerging dominant entity in patients with autoimmune myositis presenting with pure polymyositis phenotype. *Medicine.* 96, 3 (2017).
11. Petiot P, Chourmert A, Hamelin L *et al.* Necrotizing Autoimmune Myopathies. *Revue. Neurologique.* 109, 8–9 (2013).
12. Zong M, Malmstrom V, Ingrid E. Anakinra effects on T cells in patients with refractory idiopathic inflammatory myopathies. *BMJ journals. Annals of Rheumatic Diseases.* 70(2) (2011).