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Anti-HMGCR antibody-associated myositis without prior exposure to statins – A case report

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Abstract

Immune-mediated necrotising myositis (IMNM) is a specific subtype of idiopathic inflammatory myositis. The formation of anti-3-Hydroxy-3-Methylglutaryl-Co-A Reductase (HMGCR) antibodies in people exposed to statins is a rare cause of IMNM. It is much rarer for a patient who has never taken statins to have anti-HMGCR antibodies.

This case report presents a woman in her mid-30s with symmetrical proximal muscle weakness in her lower limbs and who was diagnosed with statin naïve HMGCR-associated IMNM. She had never taken statins before, but had been on aripiprazole and olanzapine sequentially for schizophrenia. She was treated with three courses of intravenous immunoglobulin, along with methotrexate, azathioprine, and prednisolone, with clinical improvement.

This case report emphasises the importance of suspecting anti-HMGCR antibody myositis in patients without exposure to statins.

Key words: immune myositis, necrotising myositis, HMGCo-A Reductase Antibody, olanzapine, aripiprazole

Introduction

Idiopathic inflammatory myopathies (IIM) are a group of diseases resulting from immune-mediated muscle inflammation and damage triggered by myositis-specific or associated antibodies. Over 15 antibodies have been identified related to this condition. Some of the antibodies include anti-synthetase antibodies (such as anti-Jo, anti-PL7, and anti-PL12), dermatomyositis-specific autoantibodies (like anti-Mi-2, anti-NXP2, anti-MDA5, and anti-TIF1), and overlap myositis antibodies (including anti-PM/Scl and anti-U1-RNP). Each antibody influences a distinct clinical phenotype characterised by a combination of muscle weakness with elevated creatine kinase (CK) levels, skin rash, arthritis, and interstitial lung disease.[1]

Immune-mediated necrotising myopathies (IMNM) are a distinct subgroup of IIM. Three subtypes of IMNM have been described based on the presence or absence of autoantibodies against signal recognition particles (SRP) or 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGCR) antibodies. Anti-HMGCR antibodies, which are against an essential enzyme involved in cholesterol synthesis, have recently been identified as a rare cause of IMNM. It is produced in patients exposed to statin, a commonly prescribed medication for dyslipidaemia. Statins upregulate the expression of HMGCR in muscle cells, which might cause an immune response against it.[2] It is even rarer to identify anti-HMGCR antibodies in patients who have not previously taken statins, where immunogenetic and environmental risk factors may play a significant role where the mechanism is not understood.[2]

We present a case of anti-HMGCR antibody-mediated IMNM, in a woman in her mid-30s who was statin naive.

Case presentation

A 36-year-old woman presented with muscle weakness for six months. She had progressive difficulty in climbing stairs. However, she did not report any associated muscle pain, muscle fatigue, difficulty in swallowing, weakness in upper limbs, or neck muscle weakness. She denied any history of fever, weight loss,

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loss of appetite, hair loss, red eyes, oral ulcers, joint pains, skin rash or Raynaud's phenomena. Her bowel and urinary habits were normal. Her family history was unremarkable. She has not had any past surgeries. She did not consume alcohol or tobacco.

She was diagnosed with schizophrenia eight years ago, which was initially managed with aripiprazole and later switched to olanzapine about a year ago. Apart from olanzapine and aripiprazole, she wasn't prescribed any other medications over the last few years. She denied consuming a predominant mushroom containing diet. Before her muscle weakness developed, she had no history of COVID-19 infection, but she received four doses of COVID-19 vaccines a few years ago.

On examination, she was hemodynamically stable and BMI was 25.4 kg/m^2. Her lungs were clear, and abdomen was soft without organomegaly. There were no anterior neck lumps or peripheral lymph node enlargements. Other findings of autoimmune connective diseases such as alopecia, rash, mouth ulcers or synovitis were absent.

Her lower limb proximal muscle power was 3/5, her upper limb proximal muscle power was 4+/5, and her weakness was symmetrical. Distal limb muscle power and neck muscle power were normal. There was no muscle fatigability. The rest of the neurological examination is unremarkable, without any cranial nerve palsies, cerebellar signs or sensory impairments.

Her initial serum creatinine kinase (CK) was 13000 u/L. Full blood count, inflammatory markers, erythrocyte sedimentary rate (ESR), and C-reactive protein (CRP) were within normal limits and her renal function remained normal throughout the course of her illness. Urinary myoglobulin was not detected.

To screen for an underlying malignancy, we performed a PET-CT of the chest-abdomen-pelvis which was reported as normal. Autoantibodies, including antinuclear antibody (ANA), extractable nuclear antibody (ENA), anti-double-stranded DNA (anti-dsDNA), and anti-neutrophil cytoplasmic antibody (ANCA), were all negative. Complement levels were normal. The extended myositis panel, which included anti-Jo, Ro-52, anti-PL7, MDA5, anti-NXP2, anti-PM/Scl, anti U1-RNP, anti-Ku, anti-Mi2, TIF-Gamma, SAE-1 and anti-SRP, also returned negative results. However, the anti-HMGCR antibody test was positive, with a value exceeding 200 CU/mL (normal values are up to 20 CU/mL).

The MRI of the whole body revealed muscle oedema compatible with myositis showing symmetrical distribution, involving multiple muscle groups, more prominent in the medial head of gastrocnemius, soleus muscles and thighs on both sides (Figure 1). The needle electromyogram (EMG) of tibialis anterior, vastus medialis, deltoid and bicep showed significant myopathic and active denervation changes without insertional activity in keeping with generalized inflammatory myopathy predominantly affecting proximal muscles, suggesting polymyositis/dermatomyositis.

The muscle biopsy (Figure 2) obtained from the quadriceps muscle showed prominent necrosis and scanty inflammation, favouring necrotising rather than inflammatory myositis.

She was treated with intravenous immunoglobulin (IVIG) and methotrexate. However, steroid therapy was not commenced due to history of schizophrenia. After receiving 3 five-day courses of IVIG within three months, the patient's CK levels stabilized.

Later, azathioprine was added to her regime due to the partial clinical and laboratory response. However, few months later the CK level went up to 6000 u/L and a prednisolone 10 mg was added to her drug regime after careful consideration of her mental illness. Her CK level stabilised around 2000 u/L with low dose prednisolone, methotrexate and azathioprine, and her muscle weakness improved completely.

Discussion

Patients with anti-HMGCR typically present with subacute, symmetrical proximal muscle weakness accompanied by significantly elevated serum CK levels. Some patients may also experience various skin manifestations and arthritis, although interstitial lung disease is rare in this group. Muscle biopsy often reveals distinctive pauci-immune necrosis of the muscle fibers. Most patients require immunosuppression early in the disease course, using corticosteroids, methotrexate, azathioprine, intravenous immunoglobulins, and rituximab.[2]

As per the diagnostic criteria of the European Neuro-Muscular Center (ENMC), anti-HMGCR associated myositis is diagnosed in a patient presenting with proximal muscle weakness, elevated serum CK levels, and positive anti-HMGCR antibodies.[3] Our patient met all the criteria for this diagnosis.

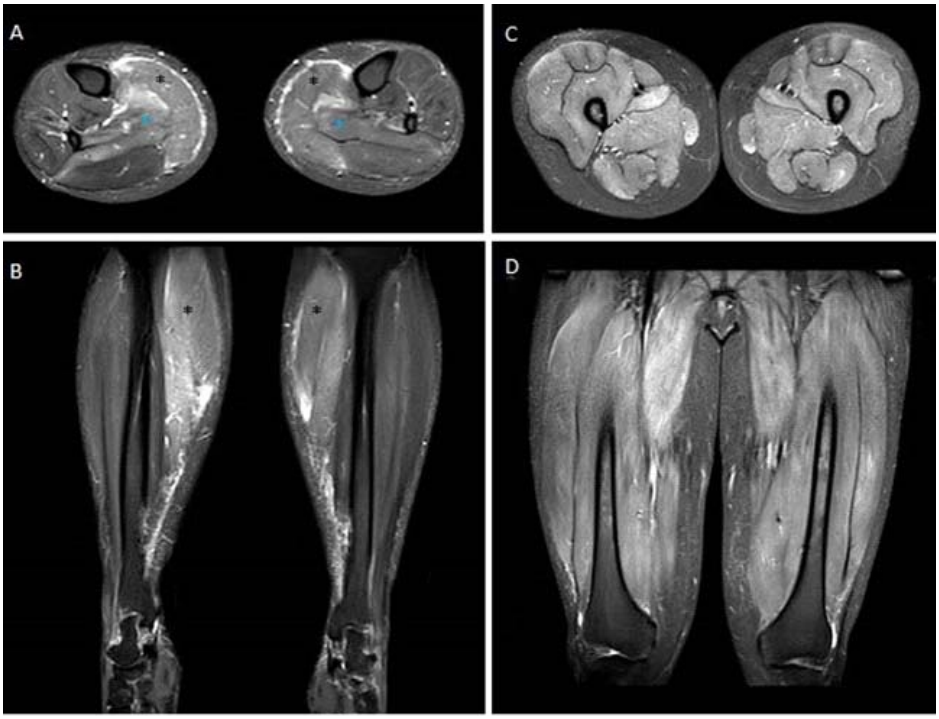

Figure 1. MRI (STIR) of lower limbs
A – axial view of calves, B – coronal view of calves, C – axial view of mid-thighs, D – coronal view of mid-thighs

There are symmetrical diffuse heterogeneous hyperintensities involving multiple muscle groups, more prominent in the medial head of gastrocnemius (black asterisk), soleus muscles (blue asterisk) and thigh muscles consistent with myositis.

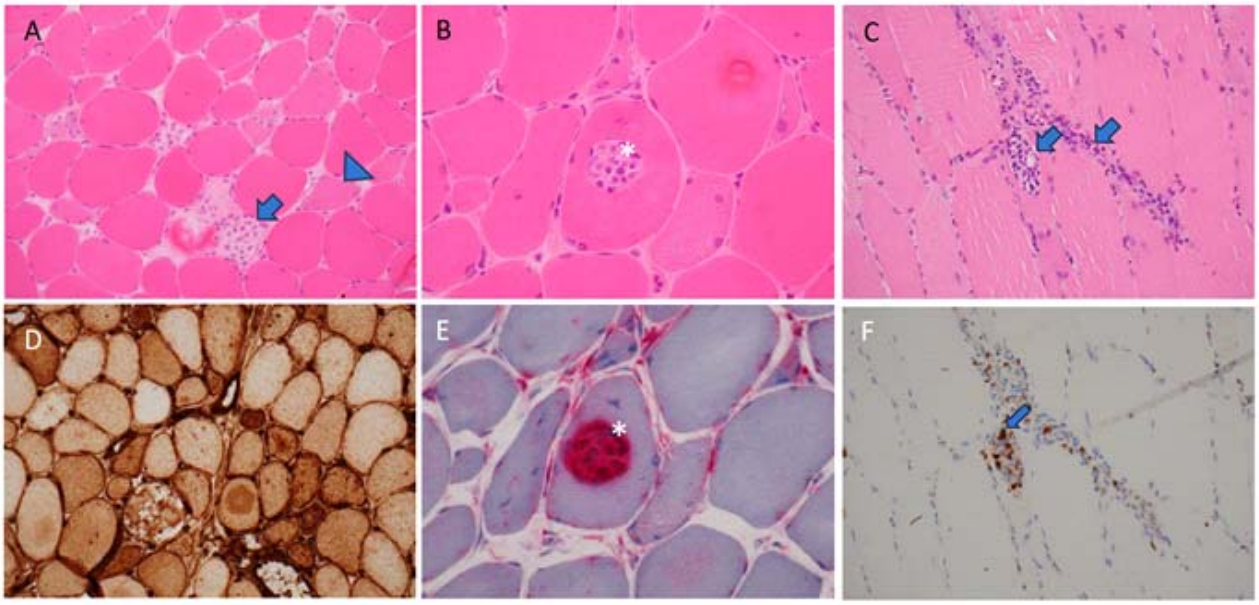

Figure 2. Histology of IMNM (Histochemistry and immunohistochemistry; A,B,D,E=frozen sections, C and F=paraffin sections):

A, HE [x 200 magnification] shows frequent necrotic and regenerative fibres (see arrow and arrowhead, respectively); B, HE [x400] illustrating invasion of macrophages in myofiber (asterisk); C, HE [x200] displaying lymphohistiocytic infiltrate (arrows); D, patchy upregulation of MHC class I [x 200]; E, Acid Phosphatase [x400] highlighting invading macrophages (asterisk); F, CD3[x200] showing minor T-cell component in lymphohistiocytic infiltrate (arrow).

Anti-HMGCR myositis in statin-naive patients is considered rare, but it has been reported more in the literature recently. In some cohorts, a significant percentage of the patients were statin naive. Such a Chinese study of IMNM associated with anti-HMGCR identified that 21% of patients had no prior exposure to statins.[4] Similarly, in a French cohort of IMNM triggered by anti-HMGCR, the majority (55%) were statin naïve.[5]

Literature suggests that certain natural products, such as mushrooms and red yeast rice, which contain natural HMGCR inhibitors may trigger anti-HMGCR myositis. Adler et al. reported a case where myositis was caused by a mushroom-based supplement regime.[6] According to the detailed dietary recall, no such dietary exposure is observed in our patient.

A few case reports suggest COVID-19 infection associated IMNM.[7] Further, there are reported cases of COVID-19 vaccination triggered IMNM.[8] Our patient had not had a COVID-19 infection before developing muscle weakness. Although she had received COVID-19 vaccinations in the past, there was no clear temporal association with her muscle weakness.

To our knowledge, there have been no reported cases of anti-HMGCR antibodies positive immune-mediated necrotizing myopathy (IMNM) associated with the use of olanzapine or aripiprazole. It is possible that one or both of these antipsychotics triggered antibody-associated IMNM in a genetically predisposed individual.

Conclusion

Clinicians should consider testing for anti-HMGCR antibody mediated myositis in patients with subacute muscle weakness and evidence of inflammatory myositis, regardless of prior statin exposure.

Author declaration

Consent

Written informed consent was obtained from the patient to publish this case report and images.

Conflict of interests

The authors declare that they have no conflict of interests.

Author contributions

HS, UP, and ES investigated the case. HS and ES planned the radiological investigation. UP and ES planned histological investigation. HS, UP, and ES were involved in forming the case report. HS and ES were involved in editing the content of the paper. All the authors approved the final version for publication.

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