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Autoimmune Anti-HMGCR Myopathy: A Rare but Disabling Complication of Statin Therapy

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Abstract

Presentation

An 85-year-old farmer developed disabling progressive proximal limb weakness and dysphagia after 10 years of statin therapy.

Diagnosis

Creatine kinase was elevated, and electromyography demonstrated myopathic abnormalities. A muscle biopsy confirmed a necrotising myopathy. Serum 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGCR) antibodies were positive. These investigations confirmed a diagnosis of autoimmune anti-HMGCR myopathy.

Treatment

The statin was stopped and treatment with steroids, intravenous immunoglobulins and rituximab yielded minimal clinical improvement over 1 year.

Conclusion

Autoimmune anti-HMGCR myopathy is a rare complication of statin therapy. In severe cases earlier treatment with multiple immunotherapies may be necessary.

Introduction

Statins are commonly prescribed medications worldwide, with Lipitor sales exceeding €100 billion between 1996 and 2011.[1] Statin-prescribing will increase significantly as over one billion people meet criteria for statin therapy based on their cardiovascular risk factors.[1] Approximately one third of Irish people aged 50 years or older were taking statins in a nationally representative sample.[2]

Statin-associated muscle symptoms (SAMS) occur in 7-29% of people taking statins and result in an approximate 75% discontinuation rate.[3,4] SAMS manifest as symmetrical pain, stiffness or cramps but are rarely associated with weakness or raised creatine kinase (CK) .[5]

Myopathy associated with 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGCR) antibodies should be considered in patients on statins who develop weakness and hyperCKemia.[6] Prompt recognition is crucial, as early statin discontinuation and treatment with immunomodulating agents results in better outcomes.[6]

We describe an 85-year-old man with anti-HMGCR myopathy that responded poorly to late immunotherapy, to raise awareness of this disabling complication.

Case Report

An 85-year-old farmer presented with progressive weakness of his limbs. Initially, he had difficulty lifting his legs when climbing into his tractor. Relevant medical history included ischaemic heart disease, hypercholesterolemia, atrial fibrillation and an intracranial aneurysm treated neurosurgcially. His medications included aspirin, telmisartan, bendroflumethiazide, metoprolol and 10 years of atorvastatin 80mg daily.

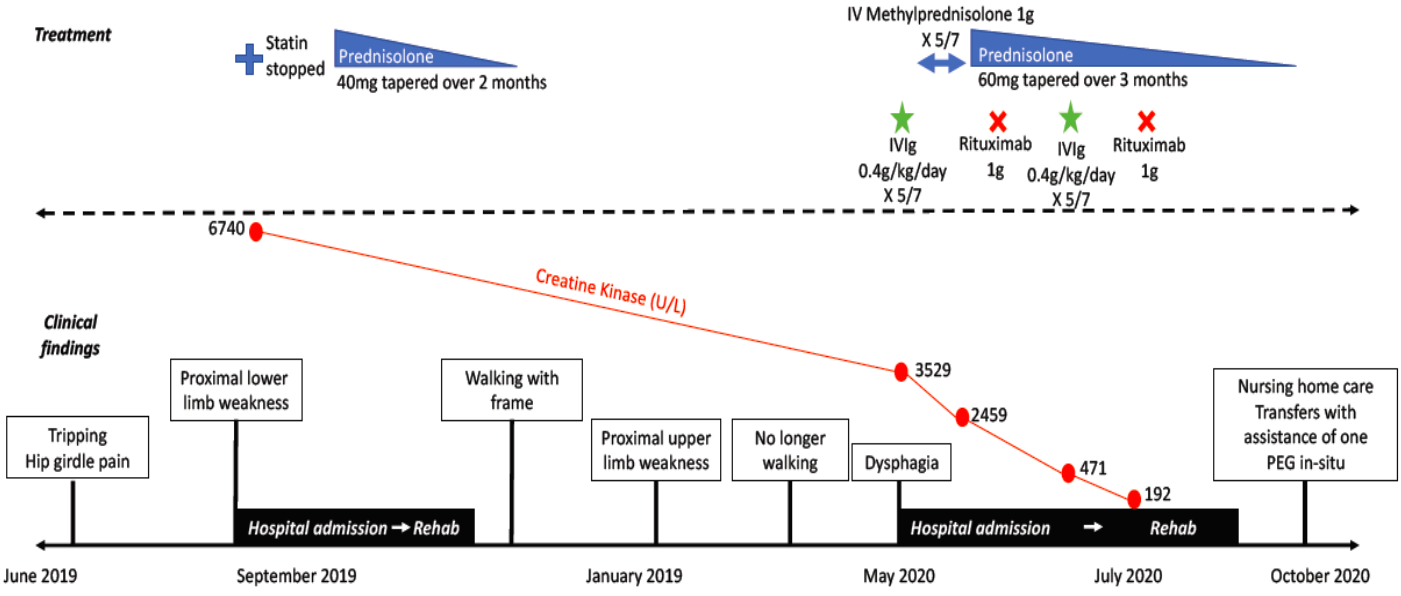
He was admitted to his local hospital following a fall. Proximal lower limb weakness was noted and CK was elevated at 6740 U/L (39-308). An inflammatory myositis was presumed but a muscle biopsy was not performed Atorvastatin was discontinued, prednisolone 40mg daily was started and tapered over two months (Figure 1).

His condition worsened and he required a frame to walk short distances. After six months, he was unable to lift his arms above his head. After nine months, he was bedbound and dysphagic (Figure 1). He was transferred to our hospital for further investigations and management.

He had symmetrical, predominantly proximal upper and lower limb weakness. Neck extension was moderately weak, with relative sparing of neck flexion. Reflexes were globally diminished. Sensory exam was normal except for reduced vibratory sensation to the ankles. Cranial nerves were unremarkable except for a soft voice and slow tongue movements.

CK was elevated at 3529 U/L. C-reactive protein and erythrocyte sedimentation rate were within normal limits. Electromyography showed myopathic motor units and fibrillation potentials. A muscle biopsy showed a necrotising myopathy (Figure 2). A myositis antibody panel was sent. A CT scan of thorax, abdomen and pelvis revealed no occult malignancy.

He was treated with intravenous steroid followed by an oral taper. He then received two courses of intravenous immunoglobulins (IVIg). Later, HMGCR antibodies returned positive (titre >200), confirming the diagnosis of anti-HMGCR myopathy and rituximab was commenced (see Figure 1 for doses). A percutaneous endoscopic gastrostomy was inserted. He partially improved (transferring from bed to chair with assistance) and resides in a nursing home.



(IV = intravenous; PEG = percutaneous endoscopic gastrostomy; IVIg = intravenous immunoglobulins; g = gram; kg = kilogram).

Figure 1: Patient's clinical timeline demonstrating progression of symptoms, creatine kinase trajectory and treatments.

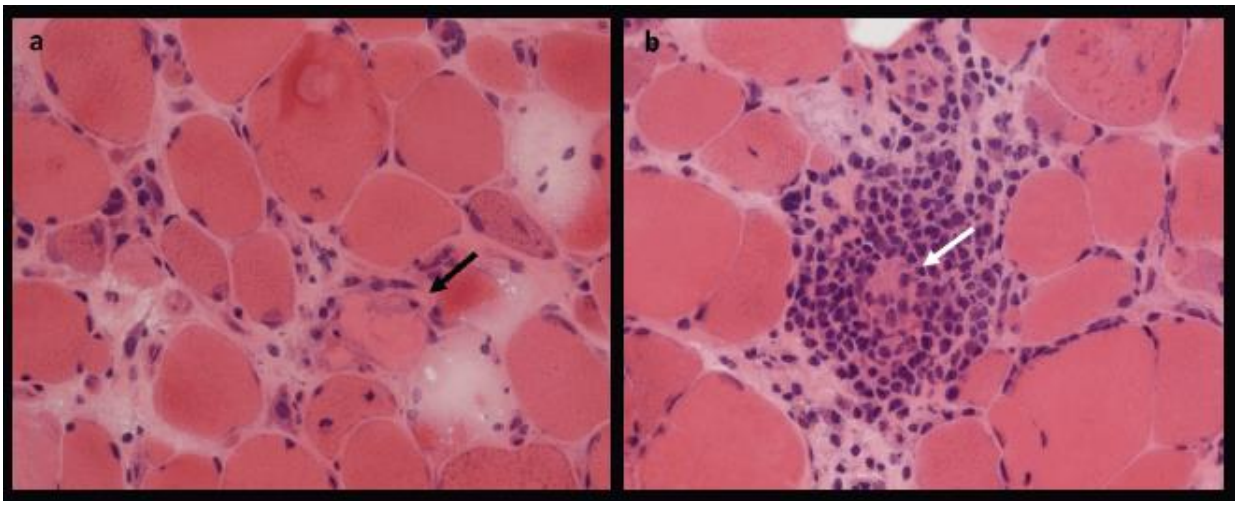


Figure 2: Muscle biopsy (vastus lateralis), necrotising myopathy.

(a) Severe variation in fibre size and increased endomysial connective tissue on a haematoxylin and eosin (H&E) stained frozen section (20X). The black arrow denotes a necrotic myofibre and myophagocytosis. **(b)** Endomysial lymphocytic inflammation (proven to be CD3 positive T cells) centred on a necrotic myofibre (white arrow) in a H&E stained section (H&E 20X). Additional immunohistological findings included variable MHC-1 upregulation in non-inflamed fibres.

Discussion

Anti-HMGCR myopathy is a rare complication of statins, with an estimated incidence of 2-3 per 100,000 on statins annually.[5] However, as statins are commonly prescribed[1], the overall incidence of anti-HMGCR myopathy is probably greater than expected. Statins upregulate muscle HMGCR and overexpression may lead to autoimmunity against HMGCR in susceptible people. The class II HLA allele DRB1*11:01 is strongly associated with developing HMGCR antibodies.[5]

Patients present with progressive proximal weakness and sometimes dysphagia.[6] Muscle-cell necrosis is seen on biopsy.[6] CK often exceeds 2000 U/L.[6] Screening for malignancy is recommended, as cancer occurs in over 15% of patients.[7] Remarkably, approximately one third of patients with HMGCR antibodies are statin-naïve.[6,8] HMGCR antibodies are rarely detected in patients with SAMs only.[9]

Immunotherapies are indicated if there is significant weakness or when minimal improvement occurs after statin discontinuation.[5] Steroids are recommended initially, followed by IVIg and/or an oral immunosuppressant such as methotrexate or azathioprine.[5] Rituximab is recommended in severe cases.[10]

Triple therapy with steroids, IVIg and an oral immunosuppressant or rituximab was used in almost half the cases reported[5] and was associated with better outcomes.[6] Over 75% of cases improve on immunotherapies, with extended treatment recommended as 55% relapse over time.[6]

Our patient's older age, along with the delayed diagnosis and treatment probably contributed to irreversible muscle injury. Clinicians are accustomed to managing SAMs but may be less familiar with the potentially devastating consequences of anti-HMGCR myopathy, and this may have contributed to the delayed diagnosis. Patients should be counselled on initiation of statin to report any muscle cramps, tenderness or weakness during treatment. They should be informed that up to one-third of patients on statins experience SAMs and that more sinister myopathic presentations are exceedingly rare. Patients on statins who develop significant weakness or hyperCKemia (CK elevated >5 times upper limit of normal) should be referred for specialist assessment by neurology or rheumatology, especially if these features persist following statin discontinuation.

This case highlights the significant side effect profile of statin therapy and in particular, the immune-mediated mechanism responsible for rare cases of statin-associated myotoxicity, that typically persists after the statin is removed. As statins are so frequently prescribed, it is important for clinicians to recognise this syndrome, to understand its immunopathogenesis and to treat early and aggressively with immunosuppressive therapies.

Declaration of Conflicts of Interest:
The authors report no potential conflicts of interest.

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References:

1. Ioannidis JP. More than a billion people taking statins? Potential implications of the new cardiovascular guidelines. *JAMA.* 2014;311(5):463-464.
2. Murphy C, Bennett K, Fahey T, Shelley E, Graham I, Kenny RA. Statin use in adults at high risk of cardiovascular disease mortality: cross-sectional analysis of baseline data from The Irish Longitudinal Study on Ageing (TILDA). *BMJ Open*. 2015;5(7):e008017.

3. Stroes ES, Thompson PD, Corsini A, Vladutiu GD, Raal FJ, Ray KK, et al. Statin-associated muscle symptoms: impact on statin therapy-European Atherosclerosis Society Consensus Panel Statement on Assessment, Aetiology and Management. *Eur Heart J.* 2015;36(17):1012-22.
4. Chodick G, Shalev V, Gerber Y, Heymann AD, Silber H, Simah V, et al. Long-term persistence with statin treatment in a not-for-profit health maintenance organization: a population-based retrospective cohort study in Israel. *Clin Ther*. 2008;30(11):2167-79.
5. Mammen AL. Statin-Associated Autoimmune Myopathy. *N Engl J Med*. 2016;374(7):664-669.
6. Kassardjian CD, Lennon VA, Alfugham NB, Mahler M, Milone M. Clinical Features and Treatment Outcomes of Necrotizing Autoimmune Myopathy. *JAMA Neurol*. 2015;72(9):996-1003.
7. Allenbach Y, Keraen J, Bouvier AM, Jooste V, Champtiaux N, Hervier B, et al. High risk of cancer in autoimmune necrotizing myopathies: usefulness of myositis specific antibody. *Brain*. 2016;139(Pt 8):2131-5.
8. Werner JL, Christopher-Stine L, Ghazarian SR, Pak KS, Kus JE, Daya NR, et al. Antibody levels correlate with creatine kinase levels and strength in anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase-associated autoimmune myopathy. *Arthritis Rheum.* 2012;64(12):4087-93.
9. Mammen A, Pak K, Williams E, Brisson D, Coresh J, Selvin E et al. Rarity of anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase antibodies in statin users, including those with self-limited musculoskeletal side effects. *Arthritis Care & Research*. 2012;64(2):269-272.
10. Landon-Cardinal O, Allenbach Y, Soulages A, Rigolet A, Hervier B, Champtiaux N, et al. Rituximab in the Treatment of Refractory Anti-HMGCR Immune-mediated Necrotizing Myopathy. *J Rheumatol*. 2019;46(6):6.