Hong Kong College of Physicians
Case report for Interim Assessment
Specialty Board of Advanced Internal Medicine (AIM)

For AIM Training, case reports should be submitted in the prescribed format together with the application form for Interim Assessment at least EIGHT Weeks before the date of Interim Assessment

Name of candidate (print and sign):
Hospital and Unit: Specialty:
Name of supervisor (print and sign):
Date(s) and place (hospital) of patient encounter: August-September 2021
Date of report submission: 11th March 2022

Case report

Note: Failure to follow the prescribed format (including the number of words) results in a FAILURE mark (score between 0 and 4) for the Case Report.

Title: A case of statin-associated immune mediated necrotising myopathy

Case history:

Mr. A is a 58-year-old Chinese man with a known history of diabetes mellitus and hyperlipidaemia, for which he attends follow-up at the general outpatient centre (GOPC). His regular medications included metformin 500mg twice daily and atorvastatin 40mg daily. However, his atorvastatin was stopped one month prior by the GOPC due to elevated liver transaminases. He was independent in his activities of daily living, worked as a security guard, and did not smoke or drink.

He was admitted to our unit for a minor traumatic head injury due to a fall, precipitated by bilateral lower limb weakness. He complained of fatigue and progressive symmetrical proximal muscle weakness for three months. His mobility soon became limited, with difficulty even upon standing up from a chair. He also complained of dysphagia to solid foods for a similar duration, subsequently losing 20 pounds over three months. He was previously referred to a general surgeon for the dysphagia, and an oesophago-gastro-duodenoscopy (OGD) done one month prior to admission showed multiple gastric antral ulcers. Histology revealed *Helicobacter*-associated chronic active gastritis without evidence of

dysplasia or malignancy, and he was given a course of eradication therapy. There was no fever, no history of syncope, chest pain or dyspnoea. He denied abdominal pain or per-rectal bleeding and did not complain of joint pain or rashes.

Physical examination showed marked muscle wasting over the shoulders, biceps, pelvis and quadriceps muscles with symmetrical proximal muscle weakness of both the upper and lower limbs, Medical Research Council (MRC) grade 3/5. There were no fasciculations or muscle tenderness. Distal limb power was full and tendon reflexes, sensation, cerebellar and cranial nerve examinations were all normal. Cardiovascular, lung and abdominal examinations were also normal.

Blood tests including complete blood count, renal function tests, cortisol and thyroid function were normal. The liver transaminases were elevated to a similar degree as previous tests (alanine transaminase 275 IU/L, aspartate transaminase 207 IU/L). Viral hepatitis markers were negative. Creatine kinase (CK) was elevated at 8261 IU/L, and there was no previous baseline level for comparison. Erythrocyte Sedimentation Rate and C-Reactive Protein were normal. Urine myoglobin and toxicology were also negative. Non-contrast computed tomography (CT) of the brain performed showed no gross intracranial abnormality.

With a working diagnosis of myopathy in mind, his statin was not resumed. Common myositis-specific antibodies were also negative. Electromyography showed features of active and chronic elements of myopathic disorder. Skeletal muscle biopsy showed active muscle fibre damage. After neurology consultation, private tests for novel autoimmune markers revealed strongly positive antibodies against 3-hydroxy-3-methylglutaryl-coenzyme A reductase (anti-HMGCR antibody). Contrast CT of the thorax and abdomen done for malignancy screening showed no evidence of malignancy. Tumour markers were normal. He was also assessed by an Ear-Nose and Throat (ENT) surgeon and did not have any significant ENT pathology. Follow up OGD showed the previous gastric ulcers had healed.

He was treated as anti-HMGCR antibody associated immune mediated necrotising myopathy, and was co-managed by the neurology and rheumatology teams. He was started on oral prednisolone at 1 milligram

per kilogram body weight (kg), and intravenous immunoglobulin (IVIg) infusion at 2 grams per kg. There was an initial improvement in the CK level, which later showed some rebound up to 5070 IU/L [Figure 1], however he showed improved muscle power to MRC grade 4/5 and his swallowing function normalised. He was discharged uneventfully after 38 days and planned for a 6-month course of monthly IVIg.

In addition to the IVIg, the patient's corticosteroids were also gradually tapered in the neurology outpatient clinic, and azathioprine was added as a steroid-sparing agent. Due to steroid use, his glycaemic control deteriorated, so linagliptin was also added. His limb power and CK levels returned to normal [Figure 1] and upon the completion of IVIg, he was referred to the rheumatology clinic for long term follow up.

Discussion and literature review

Ever since the reduction of low-density lipoprotein cholesterol (LDL-C) was demonstrated to improve cardiovascular morbidity and mortality, statins have become a commonly used class of lipid-lowering drugs for both primary and secondary prevention of cardiovascular disease [1]. Statins achieve this through competitive inhibition of hydroxymethylglutaryl-coenzyme A reductase (HMGCR), the rate limiting enzyme in hepatic cholesterol synthesis. The reduced cholesterol production results in increased LDL receptor expression on the hepatocyte cell surface, and thus increased uptake of LDL from the blood with decreased plasma levels of LDL-C. The degree of LDL reduction is dose-dependent and although it differs between different statins, the overall benefit of statin treatment demonstrates a class effect by absolute reduction in the LDL-C.

Statin-associated muscle symptoms (SAMS) remain a major cause for treatment non-adherence or discontinuation, reportedly affecting 10% of patients in observational studies [2]. SAMS may range from asymptomatic elevations in CK, myalgia or weakness, myositis and rhabdomyolysis. Indeed, a meta-analysis revealed that in the case of mild musculoskeletal symptoms, the incidence was similar between the statin and placebo groups [3], but serious statin-induced muscle damage can occur in 1 in 10,000 patients [4]. Despite SAMS being the most prevalent adverse effect associated with statin therapy, routine monitoring of CK levels is not recommended; a retrospective study of

over 1000 patients in primary care showed no significant CK value abnormalities potentially related to use of statins [5]. Instead, patients should be adequately counselled on the potential SAMS, and a baseline CK level before initiation of treatment for reference may be more useful in the event of symptoms developing. Risk factors for SAMS include use of lipophilic statins, high-dose statins, female sex, increased age, underlying liver or renal disease, low body mass index, vitamin D and calcium disorders and concomitant use of medications metabolised by the hepatic cytochrome P450 enzyme. The majority of patients with SAMS recover after cessation of the statin; however, as highlighted in the case above, a small fraction may develop the exceptionally rarer side effect of statin-associated immune mediated necrotising myopathy.

Statin-associated immune mediated necrotising myopathy (HMGCR IMNM) is estimated to affect approximately 2-3 in 100,000 patients on statins [4]. There are no identifiable risk factors for the development of statin-associated IMNM, unlike those described for other SAMS phenotypes. Furthermore, it can unpredictably present months to several years after initiating statin therapy. In the case above, the patient had received statins for 6 years before his symptoms developed.

HMGCR IMNM presents with subacute symmetrical proximal muscle weakness with markedly elevated CK (> 10 times the upper limit of normal) in nearly 90% of cases [4]. Other reported symptoms include truncal weakness, facial weakness, dysphagia, fatigue, and weight loss. Not only do these symptoms overlap with other SAMS manifestations, but also other idiopathic inflammatory myopathies, infective, toxic or metabolic myopathies, muscular dystrophies and diseases affecting the neuromuscular junction to the spinal anterior horn cells. Therein lies the challenge in diagnosing IMNM, and thus, systematic evaluation and a high index of suspicion is needed for prompt diagnosis and management.

Electromyography shows non-specific irritable myopathy features, which cannot be distinguished from other inflammatory myopathies. Muscle biopsy demonstrates muscle fibre necrosis with macrophage infiltration. The advent of detecting autoantibodies against HMGCR via enzyme-link immunosorbent assay generated a marker that is both sensitive and specific. One study showed 24 of 26 patients (92%) with clinical presentations compatible with HMGCR IMNM were positive for

anti-HMCGR antibodies and had taken statins before their disease onset [6]. Furthermore, it has not been detected in patients on statins who do not have muscle disease or only develop self-limiting statin-induced myopathy, thus supporting a high negative predictive value for this test. Nonetheless, anti-HMGCR antibodies have also been detected in statin-naïve patients or in those with IMNM and an underlying malignancy. In 2016, the European Neuromuscular Centre recommended such patients to undergo malignancy screening [7].

The pathophysiological mechanisms of HMGCR IMNM remain poorly understood. It is proposed that statins trigger an overexpression of HMGCR in muscle and tissue cells after exposure in genetically susceptible people, leading to the development of HMGCR autoimmunity. The high levels of HMGCR in regenerating muscle cells continue to perpetuate an autoimmune response, which continues even after cessation of statin [4,8]. An HLA allele, DRB1*11:01, was found to be strongly associated with the development of anti-HMGCR autoantibodies, even in patients without exposure to statins. However, the majority of those with this allele do not develop autoimmunity after treatment with statins, suggesting that other multifactorial genetic and environmental factors likely have a role [4].

Immediate discontinuation of statin is warranted in HMGCR IMNM, but alone is often insufficient to reverse the disease course, with persistence of CK elevation and muscle weakness. Treatment with immunosuppressants is usually warranted, although, due to a lack of prospective studies, treatment strategies are largely based on case series and expert opinion. Recommended first-line treatment includes high dose prednisolone or pulsed IV methylprednisolone plus a steroid sparing agent such as azathioprine, methotrexate, mycophenolate mofetil, cyclosporine or cyclophosphamide. Combination therapy has also been described. IVIg should be considered in patients with severe disease or refractory disease at 8-12 weeks. Case studies have also supported the use of IVIg as first-line therapy monotherapy, especially in those with pre-existing diabetes, as with the above patient [4,7,9]. In refractory cases, rituximab has emerged as a potential third-line agent for patients who show persistent muscle weakness or disease relapse.

Although long term immunotherapy is usually required to prevent

disease relapse, most cases demonstrate symptom resolution, especially in those who receive early therapy. Immunosuppressants can then be tapered accordingly with close monitoring for symptom relapse. It is not recommended to rechallenge patients with HMGCR IMNM with statins. Instead, reinforcement of lifestyle modifications and alternative lipid lowering agents can be considered to achieve LDL-C targets.

In conclusion, IMNM is a rare but devastating side effect of statin therapy, and often cessation of statin alone is insufficient to reverse the clinical and biochemical abnormalities. Additional treatment with immunosuppressants and steroids are usually required for disease control, and alternative lipid-lowering agents should be considered in those whom are indicated for high intensity LDL-C control.

Tables and figures (where applicable) (no more than two figures)

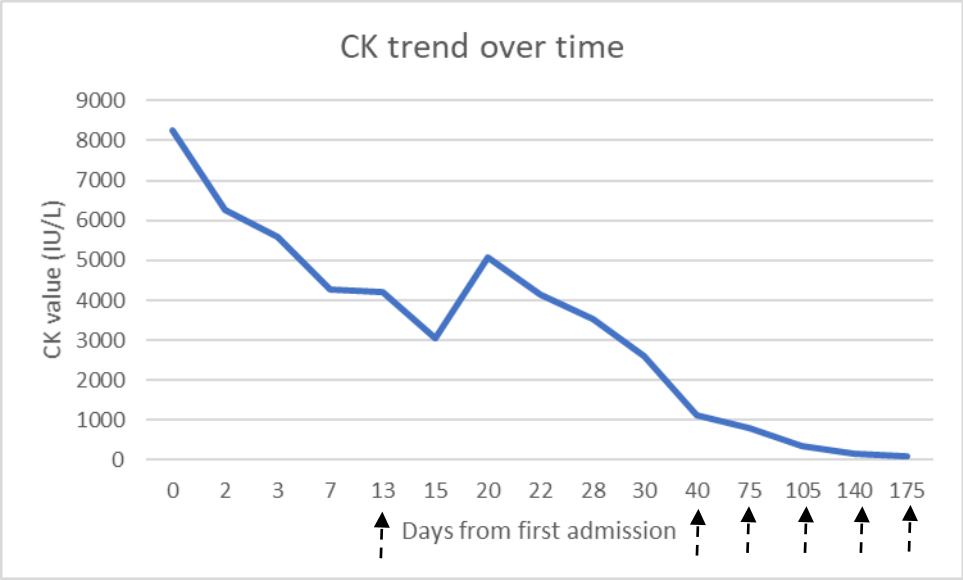

Figure 1: CK level trend over time. Arrows represent days IVIg administered

Reference (not more than 10)

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No of words in Case History and Discussion (excluding references): 1665

(should be between 1000-2000)

Declaration

I hereby declare that the case report submitted represents my own work and adheres to the prescribed format. I have been in clinical contact with the case selected. The case report has not been submitted to any assessment board or publication and it is NOT related to my second specialty(ies), if any. My consent is hereby given to the College to keep a copy of my case report, in written and/or electronic, at the College Secretariat and allow the public to have free access to the work for reference.

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Endorsed by Supervisor *

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