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): Wong Sum Lung
Hospital and Unit: Department of Medicine, QMH Specialty: Medical Oncology and AIM
Name of supervisor (print and sign): Dr Shea Yat Fung
Date(s) and place (hospital) of patient encounter: 24/2/23 to 31/3/23 in TWH
Date of report submission: 11/9/2023

Case report

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

Title: A case of immune mediated necrotizing myopathy

Case history:

Presentation

A 37 year old man of good past health presented with proximal muscle weakness and dysphagia to a Macau hospital in early 2021. His creatinine kinase (CK) was found to be around 12000 U/L. Electromyography and muscle biopsy were done and a diagnosis of polymyositis was made. Serology showed ANA 1 :320 and anti-SRP (signal recognition particle) antibody was positive. He was started on prednisolone 65mg and mycophenolate mofetil (MMF) 1g BD and his condition stabilized with CK dropping to ~1200, after which prednisolone was tapered to 10mg. He was also started on simvastatin afterwards for hyperlipidaemia.

The patient contracted COVID in December-2022 and MMF was temporarily withheld. Weakness and shortness of breath ensued, and he was put back on prednisolone 60 mg and MMF and referred to our cluster. Upon admission, he had proximal weakness, subjective shortness of breath and could barely stand. He denied dysphagia, choking, fever or constitutional symptoms. No supplemental oxygen was required. Examination showed loss of muscle bulk over bilateral pectoralis, deltoid and gluteus muscles. The proximal power was 3/5 and distal power was 5/5. The rest of respiratory, cardiac, abdominal and neurological examinations were unremarkable.

Investigations

The patient's chest x-ray was clear. Echocardiogram showed preserved left ventricular ejection fraction of 60%. His COVID Ct value was 42. Peak-flow rate was normal. Serum creatine kinase (CK) was 6461 U/L, lactate dehydrogenase was 780 U/L and aspartate aminotransferase was 179 U/L. Urine myoglobin was negative. He also had

neutrophilia of 14 X 10^9L and elevated alanine aminotransferase of 200 U/L, possibly related to
prednisolone. Otherwise, blood counts, liver, renal and thyroid function tests were all normal, so were his troponin, erythrocyte sediment rate (ESR), C-reactive protein (CRP) and hepatitis B/C workup. Serology showed that anti-SRP antibody was positive, while antinuclear antibody (ANA), anti-extractable nuclear antigen antibodies (ENA), C3, C4, immunoglobulin pattern and anti-HMGCR (3-hydroxy-3-methylglutaryl coenzyme A reductase) antibody were all normal. A whole body positron emission tomography-computed tomography (PET-CT) to rule out malignancy was negative. Upper airway screening by endoscopy and swallowing assessment were both unremarkable.

Treatment

A diagnosis of anti-SRP immune mediated necrotizing myopathy (IMNM) was made. He was continued on prednisolone 60 mg and MMF 1g BO. However, his power did not improve and CK only dropped to ~3000.
Intravenous immunoglobulin (IVIg) was then given at a dose of 30g per day for two courses and CK dropped to ~600 U/L. After a course of rehab, his power improved to 4/5 over proximal muscles and he was able to walk unaided. He was discharged with prednisolone 15 mg daily and MMF 1g BD. Unfortunately, upon follow-up, his required a walking stick again and CK rebounded to 2300. Despite two doses of rituximab, his condition remained static as of the writing of this report.

Discussion and literature review

Idiopathic inflammatory myopathies (IIM), generally known as myositis, have undergone significant changes in sub-classification in recent years. Historically, IIM were classified into inclusion body myositis (IBM), dermatomyositis (DM) and polymyositis (PM), with PM defined by its lack of cutaneous features or characteristic muscle biopsy findings. In recent years, the discoveries of new autoantibodies and heterogenous pathological findings have allowed PM to be further differentiated and cease to exist as a specific entity[l]. In fact, the latest classification divides IIM into 4 entities: OM, IBM, antisynthetase syndrome and IMNM[l]. Antisynthetase syndrome is defined by autoantibody against aminoacyl-transfer RNA synthetase and presents with myopathy, interstitial lung disease (ILD), arthritis, Raynaud phenomenon and skin changes such as 'mechanic's hands'. In contrast, the presentations of IMNM mainly relates to myopathy. IMNM can be divided into 3 subtypes by serology: anti-SRP antibody positive, anti-HMGCR antibody positive, and seronegative IMNM[2].

Though different subtypes have variations of presentations, IMNM consistently presents as proximal muscle predominant weakness. The onset is usually acute (within weeks) or subacute (<6 months), but slowly progressive onset (over years) has also been reported exclusively in seropositive IMNM[2]. Muscle atrophy is frequent, neck weakness and dysphagia are often reported, and respiratory insufficiency is possible[3]. In general, symptoms are more severe for anti-SRP compared to ant i-

HMGCR IMNM[3]. In addition, extra-muscular manifestations are rare in anti-HMGCR and seronegative IMNM but are found in anti-SRP IMNM[2]. The main concern is myocarditis, with around 2-40% of anti-SRP patients having cardiac symptoms or abnormal investigation results including electrocardiogram or cardiac imaging[2]. ILD is also frequent (up to 40%). However, most patients are asymptomatic and have normal lung function tests, and the diagnosis is mostly purely radiological. Other features, such as skin involvement, are uncommon (<10%)[2].

IIM and IMNM are rare diseases. The incidence of IIM is around 2.4-33.8 per 100000[2]. As IMNM is a novel entity, its incidence is difficult to establish[4]. It is estimated that 5- 15% of all IIM patients are positive for anti-SRP, and 6-10% are positive for anti-HMGCR[2, 3]. Overall, anti SRP IMNM consists of around 20-40% of IMNM; and seronegative IMNM around 10-12% of all IMNM[2]. The median age of onset is 40 and 55 for anti-SRP and anti-HMGCR IMNM respectively, with pediatric cases also being reported[4]. A female preponderance is generally observed. Coexistence of other rheumatological disease is only observed in a small minority of cases and is not usually regarded as a significant risk factor[2, 3]. In fact, as of now, few risk factors for anti-SRP IMNM have been identified. For anti-HMGCR IMNM, there exists theoretical and epidemiological associations with statin use. The autoantibody shares the same target as statins, and a history of statin use is reported much more frequently than in anti-SRP IMNM patients[4].
Mechanistically, statins are known to upregulate HMGCR and are also myotoxic. Thus, statins may cause initial muscle damage and expression of antigen targets such as HMGCR, which in turn induce autoimmune responses in patients who are genetically predisposed to present such epitopes[2]. Interestingly, a specific MHC class II allele (DRB1 *11:01) is strongly associated with anti-HMGCR IMNM, with an odds ratio of 3.7 in Asians and up to 56.5 in Western populations[4]. However, the reported statin exposure varies considerably by geography, ranging from 14-38% in Asian cohorts to up to 63% in Western cohorts[2, 4]. The age of onset of non-statin-exposed patients is 40, considerably younger than statin-exposed patients and similar to anti-SRP patients, suggesting that these may be distinctive populations[4]. Lastly, an association with cancer exists for seronegative IMNM, with a French cohort reporting a 21 % incidence of malignancy within 3 years before or after a seronegative IMNM diagnosis, which is significantly increased compared to the general population[5]. In contrast, the association with cancer of seropositive IMNM is controversial, with some reports suggesting that anti-HMGCR patients having a slightly higher risk[2, 5].

The workup for suspected IMNM starts with measuring serum CK, which in most cases are grossly elevated (> = 30 times of normal) regardless of subtype. CRP and ESR are often normal [6]. Thyroid function tests and testing for hepatitis B, C and human immunodeficiency virus should be done to exclude other causes of myopathy and, for viral testing especially, to ensure treatment safety, Autoantibodies including anti-SRP and anti-HMGCR antibodies testing is essential. As anti-SRP and anti-HMGCR are specific for IMNM, a diagnosis can already be established in patients who are positive and possess typical clinical presentations and elevated CK[2, 3]. Magnetic resonance imaging (MRI) of skeletal muscles may show generalized muscle edema,

atrophy, and fatty infiltration [2]. Muscle biopsy, if required (such as in seronegative IMNM), would be expected to demonstrate the pathological hallmarks of IMNM: widespread necrosis of myofibers with different stages of necrosis, myophagocytosis and regeneration; as well as paucilymphocytic infiltrates[1, 2, 4]. Finally, screening for possible impending respiratory failure (by spirometry), myocarditis in anti-SRP IMNM, and malignancy in anti-HMCGR and seronegative IMNMs are required[2].

Anti-SRP and anti-HMGCR antibodies are directly pathogenic, and their titers are correlated to patients' CK levels and muscle strength[2]. Both proteins are ubiquitously exposed on the ER surface in all cells and are not usually 'targetable' due to their location. However, in certain conditions, SRP and HMGCR reach the surface of regenerative myofibers and become targets for autoantibodies. Binding of autoantibodies induces myofiber atrophy and blocks myotube formation and muscle regeneration[2]. In addition, autoantibodies binding was thought to activate the classical complement pathway, form membrane attack complexes and cause myofiber necrosis, as evident that sarcolemmal complement deposition is a frequent feature[2]. Recently however, a trial of the CS inhibitor zilucoplan failed to improve outcomes, challenging the pathogenic role of complements and raising the, possibility that complement activation may instead be secondary to muscle! injury[7].

IMNM has worse muscle prognosis than most other types of IIM[4]. In addition, no positive clinical trial exists and treatment is mostly based on expert consensus and observation studies[2, 4, 7], Treatment is usually split into 2 phases: induction and maintenance[2, 4]. In the induction phase, corticosteroids are the cornerstone. However, monotherapy is usually insufficient (especially in anti-SRP IMNM) and most patient require a second agent, such as methotrexate, MMF, azathioprine, cyclophosphamide or calcineurin inhibitors[2, 4], If response is still suboptimal, IVIG and/or rituximab should be added. IVIg is efficacious for all subtypes, while rituximab appears to have limited utility in anti-HMGCR IMNM[2, 4]. Withdrawal of statins in anti-HMGCR IMNM is required, and proprotein covertase subtilisin kexin type 9 (PCSK9) inhibitors may be safely used instead [2, 8]. Maintenance therapy consists of tapering steroids as much as possible and continuing the second oral agent with or without rituximab for at least 2 years if the disease is well controlled[4]. Physiotherapy and rehabilitation are also essential [4]. Unfortunately, patients with IMNM, especially anti-SRP disease, often have poor recovery of muscle strength despite treatment. Only half of anti-SRP patients, and two-thirds of anti-HMGCR patients, regain near-full or full muscle strength after 4 years of
therapy, with young age(<50 years) predicting an even worse muscle recovery[2]. In addition, myocarditis and associated malignancies are major drivers of mortality[2, 5]. Finally, the chronicity of corticosteroids and other immunosuppressants often exposes patients to considerable long-term side effects[2, 4].

1In conclusion, this patient presented with typical features of anti-SRP IMNM, I a rare and rather novel disease entity. Unfortunately, as seen in our patient, the disease course is often prolonged and therapeutic options are currently
limited. Better understanding of pathogenesis, as well as prospective clinical trials, are required to improve outcomes of this devastating disease.

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

Reference (not more than 10)

1. Merlonghi, G., G. Antonini, and M. Garibaldi, Immune-mediated necrotizing myopathy (IMNM): A myopathological challenge. Autoimmun Rev, 2022. 21(2): p. 102993.
2. Allenbach, Y., et al., Immune-mediatednecrotizing myopathy: clinical features and pathogenesis. Nat Rev Rheumatol, 2020. 16(12): p. 689-701. I
3. Watanabe, Y., et al., Clinical features and prognosis in anti-SRP and anti-HMGCR necrotising myopathy. J Neurol Neurosurg Psychiatry, 2016. 87(10): p, 1038-44.
4. Pinal-Fernandez, I., M. Casal-Dominguez, and A.L. Mammen, Immune-MediatedNecrotizing Myopathy. Curr Rheumatol Rep, 2018. 20(4): p. 21.
5. Allenbach, Y., et al., High risk of cancer in autoimmune necrotizing myopathies: usefulness of myositis specific antibody. Brain, 2016. 139(Pt 8): p. 2131-5.
6. Park, J.K., et al., Pulmonary impairment, not muscle injury, is associated with elevated ESR in the idiopathic inflammatory myopathies. Rheumatology (Oxford), 2013. 52(7): p. 1336-8.
7. Mammen, A.L., et al., Zilucoplan in immune-mediated necrotising myopathy: a phase 2, randomised, double-blind, placebo-controlled, multicentre trial. Lancet Rheumatol, 2023. 5(2): p. e67-e76.
8. Tiniakou, E., et al., Use of Proprotein Convertase Subtilisin/Kexin Type 9 Inhibitors in Statin-Associated Immune-Mediated Necrotizing Myopathy: A Case Series. Arthritis Rheumatol, 2019. 71(10): p. 1723-1726.

No of words in Case History and Discussion (excluding references): 1698 (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.

_____

(signature of Trainee)

Endorsed by Supervisor *

_____

(signature of Supervisor)

* Supervisors must go over the Case Report with the Trainees, advise Trainees whether further amendments are necessary, review the Originality/Similarity Report prepared by Trainees, adherence to the required format, sign on the report and remind Trainees on issues related to copyright and plagiarism.