CASE REPORT

Immune-mediated necrotising myopathy: a rare cause of hyperCKaemia

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SUMMARY

Immune-mediated necrotising myopathy (IMNM) is a type of inflammatory myopathy characterised by acute or subacute severe proximal muscle weakness, significantly elevated creatine kinase levels, and prominent myofibre necrosis and regeneration with little or no inflammation. A subtype of IMNM identified by anti-HMG-CoA reductase (HMGCR)antibodies has been shown to be associated with statin exposure. Treatment of IMNM consists of immunosuppression with steroids, steroid-sparing agents, intravenous immune globulin and/or biologics. We present here a case of anti-HMCGR-associated IMNM and review the pathophysiology, diagnosis and treatment to increase physician awareness of this rare and debilitating condition.

BACKGROUND

Early diagnosis and treatment of immune-mediated necrotising myopathy (IMNM) can lead to significant clinical improvement; however, untreated or insufficiently treated IMNM can cause severe morbidity and mortality. This patient with IMNM was not told to discontinue his statin when his symptoms first began and initially received subtherapeutic immunotherapy. These series of suboptimal interventions, which may have resulted from inexperience with this condition, exacerbated his myopathy and severely impaired his quality of life. By writing this case report, we hope to educate physicians on the proper workup and treatment of IMNM and to highlight the importance of maintaining an appropriate level of clinical suspicion in patients with such symptoms.

CASE

A 72-year-old man with a history of hypertension, hyperlipidaemia and complete heart block with pacemaker placement initially presented to his primary care physician with complaints of generalised weakness, profound proximal muscle pain and dark urine for approximately a month. These symptoms began abruptly after the patient returned home from spending a day out in the sun at a racetrack. He was able to perform activities of daily living (ADLs) and instrumental ADLs (IADLs) independently at this time. Initial investigations included a creatine kinase (CK) level of 24 140 U/L and urinalysis strongly positive for blood but not red cell counts (table 1). A full comprehensive metabolic panel was not obtained at this time to assess liver function tests, such as aspartate aminotransferase (AST) and alanine aminotransferase (ALT). The patient was subsequently treated in the emergency department (ED) for presumptive rhabdomyolysis with intravenous fluids (IVF), CK improved to 19,990 U/L, and he was deemed suitable for discharge with instructions for oral rehydration and to return to the ED if symptoms persisted. Atorvastatin was not discontinued because he had been on a stable dose for 2 years without prior issues.

Five days later, the patient represented to an outside hospital with progressive weakness, dysphagia to solids and thin liquids with failure of a home swallow study and a CK of 40 476 U/L (table 1). He was admitted and treated for the hyperCKaemia with IVF. Atorvastatin was discontinued. Further workup included a muscle biopsy of the right thigh consistent with IMNM, a percutaneous endoscopic gastrostomy tube placement, and the patient was discharged to a skilled nursing facility (SNF) with a steroid taper.

Two and a half weeks later, the patient was admitted to our hospital from the SNF for continued deterioration. He could no longer stand, sit up or roll over in bed, was dysphagic to solids and all liquids and required assistance with all his ADLs. Physical examination revealed diffuse muscle atrophy, as reflected in his low creatinine (table 1) and symmetric proximal muscle weakness without tenderness or rash; strength was 3/5 with shoulder abduction, hip flexion, hip extension, knee flexion and knee extension. Laboratory findings were significant for a CK of 2460 U/L, lactate dehydrogenase (LDH) of 374 U/L and aldolase >56 U/L (table 1).

INVESTIGATIONS

During the patient's first hospital admission, his persistently elevated CK and worsening proximal muscle weakness, despite discontinuation of the statin, prompted his doctors to obtain a thorough inflammatory myopathy workup, which included CK of 40 476 U/L, creatine kinase-muscle/brain (CK-MB) of 284 ng/mL, AST of 1750 U/L, ALT of 839 U/L, positive antinuclear antibody (ANA) and anti-HMG-CoA reductase (HMGCR) antibody of >200 (≥60 strong positive) (table 1). Anti-Jo-1 and anti-liver-kidney microsomal antibodies were negative. Though an MRI was not obtained, the above results led to a very high suspicion for an inflammatory myopathy, and the patient was recommended to undergo a muscle biopsy directly. The muscle biopsy of the patient's right thigh showed many individual myofibres undergoing

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Table 1 Laboratory results from patient's ED visit, admissions and follow-ups.

	Creatinine (mg/dL)	CK (U/L)	AST (U/L)	ALT (U/L)	LDH (U/L)	Aldolase (U/L)
ED visit	1.03	24140	N/A	N/A	N/A	N/A
Admission #1	0.7 (low)	40476	1750	839	N/A	N/A
Admission #2	0.35 (low)	2460 (high)	284 (high)	301 (high)	374 (high)	>56 (high)
1-month follow-up	0.50 (low)	67	40 (high)	53 (high)	134	3.1
2-month follow-up	0.68	66	29	36	172	4.9

ALT alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase; ED, emergency department; LDH, lactate dehydrogenase.

degeneration with necrosis and regeneration, without significant endomysial inflammation or evidence of vasculitis (figure 1).

The clinical features of a symmetric proximal muscle weakness, in conjunction with the strongly positive anti-HMGCR antibody and muscle biopsy showing necrosis without significant inflammation, were diagnostic of anti-HMGCR-associated IMNM.

DIFFERENTIAL DIAGNOSIS

Statin-induced myopathies have been reported to occur at an incidence of 11 per 100 000 person-years.[1] Furthermore, it is imperative to recognise that statin-induced severe rhabdomyolysis with elevated CK levels of >10 000 U/L, muscle symptoms and requirement of hospital admission occurs approximately in 1.6–6.5 per 1000 000 person-years.[1] In the case of rhabdomyolysis renal impairment ensues due to acute tubular necrosis caused by myoglobin precipitation in the renal tubules, potentially leading to life-threatening electrolyte disturbances. Treatment of statin-induced rhabdomyolysis requires prompt withdrawal of the drug along with standard treatment for rhabdomyolysis, including IVF, close monitoring of electrolytes, progression of acute kidney injury and possible need for renal replacement therapy depending on the severity of the case.

The differential diagnosis for an inflammatory myopathy includes dermatomyositis, polymyositis, IMNM and inclusion-body myositis, which can be distinguished based on the pattern of muscle weakness, degree of CK elevation, electromyography and muscle biopsy findings and autoantibody markers. For example, while dermatomyositis, polymyositis and IMNM are all characterised by acute or subacute onset of proximal muscle weakness, dermatomyositis additionally presents with characteristic skin findings of periorbital rash, 'shawl sign' and/or Gottron's papules. In contrast, inclusion-body myositis typically presents as slow-onset proximal and distal muscle weakness.[2]

The findings on muscle biopsy, the site of which is guided by the presence of active inflammation on MRI, are particularly helpful. Muscle biopsies in dermatomyositis, polymyositis and inclusion-body myositis exhibit perivascular inflammation/infiltration, while those in IMNM often lack significant inflammation.[2]

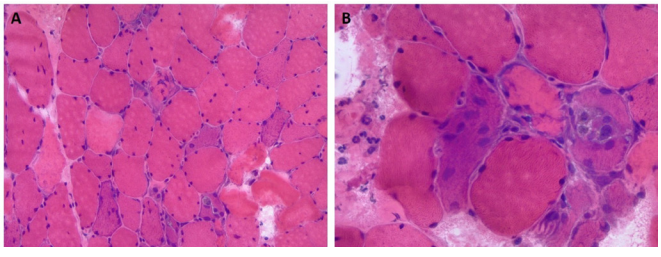

Figure 1 **(A)** Medium and (B) high-power microphotographs of the patient's muscle biopsy showing individual myofibre necrosis and regenerative basophilia without endomysial lymphocytic infiltration or evidence of vasculitis.

TREATMENT

Once biopsy results were confirmed, the patient was treated with 60 mg prednisone daily, with symptomatic improvement and downtrend in CK to 6179 U/L at discharge. The dosage was tapered down by 10 mg per week, such that the patient was taking 30 mg daily on his admission to our hospital. At the time of presentation to us, due to the patient's refractory and severe disease, he was immediately seen by rheumatology who initiated treatment with high-dose immunosuppressive therapy consisting of pulse steroids (1 g of intravenous methylprednisolone daily for 3 days) followed by intravenous immune globulin (IVIG; 0.5 g/kg for 4 days), prednisone (50 mg daily) and mycophenolate mofetil (500 mg daily), with the plan to taper the prednisone by 10 mg every 2 weeks and to increase the mycophenolate mofetil as tolerated.

OUTCOME AND FOLLOW-UP

Throughout his 4-week hospital course, the patient experienced subjective and objective improvement in his muscle strength. He could participate in therapeutic exercises, transfers and ADLs. His strength improved to 4/5 with shoulder abduction, 4/5 with hip flexion and 4/5 with knee extension. In addition, his CK, LDH and aldolase normalised (table 1). He was discharged to the acute rehabilitation unit, where he remains at the time of this report. He is being treated with prednisone 30 mg daily and mycophenolate mofetil 1000 mg twice daily and has had two additional courses of IVIG. His strength has improved to 5/5 with shoulder abduction and 4/5 with hip flexion and knee extension. He is reported to now be independent of his ADLs and ambulate with the assistance of a front wheel walker.

DISCUSSION

IMNM comprises up to 19% of inflammatory myopathies.[2] Possible mechanisms of pathogenesis include type 1 helper T cell and M1 macrophage activation leading to production of proinflammatory cytokines, upregulation of sarcolemmal major histocompatibility complex (MHC) class I and activation of antibody-mediated cytotoxicity.[3 4] Potential triggers include antisignal recognition particle (SRP), anti-HMGCR and anti-synthetase antibodies, connective tissue diseases, malignancy, viral infections and trauma.[5 6] However, IMNM can also be idiopathic.[5]

Anti-HMGCR-associated IMNM occurs in 2–3 out of every 100 000 patients taking statins, especially atorvastatin and simvastatin.[5 7] The proposed mechanism is (1) genetic susceptibility in the form of the HLA-DRB1*11:01 allele (which is associated with the development of anti-HMGCR antibodies) and (2) an environmental trigger in the form of statins, which upregulate HMGCR and by binding to HMGCR, may also lead

to an altered HMGCR conformation and thus new antigenic epitopes.[7] This HMGCR autoimmunity is then perpetuated by HMGCR overexpression in regenerating muscle, as the enzyme is required for normal myocyte differentiation.[7] Interestingly, while statin exposure is the strongest risk factor for anti-HMGCR-associated IMNM, 30%–50% of patients with anti-HMGCR-associated IMNM have never received statins, and their symptoms are more refractory to immunosuppressive treatment than those of statin-exposed patients.[7] However, as statins may be found in food sources like red yeast rice or oyster mushrooms, such patients may not be truly statin naïve[8]

The diagnosis of IMNM is based on clinical findings and targeted testing. First, in addition to acute or subacute onset of severe proximal muscle weakness, patients may also present with dysphagia, weight loss and cardiopulmonary manifestations, such as dyspnoea and arrhythmias.[5]

Second, important laboratory tests for IMNM include significantly elevated CK and anti-SRP, antisynthetase and anti-HMGCR antibodies.[5] CK is the most sensitive indicator of inflammatory myopathies.[2] Anti-HMGCR antibodies are highly sensitive and specific for IMNM, as they are rarely found in the general population, including those with self-limited statin intolerance.[9] This patient's highest CK level was greater than 100 times the upper limit of normal, and his anti-HMGCR antibody level of >200 was greater than the measurable range. It is important to note that elevations in AST and ALT may be seen, as they are present in muscle tissue, so that unnecessary liver biopsies can be avoided. Third, this patient's muscle biopsy exhibited the hallmark histopathological finding of IMNM including myofibre necrosis and regeneration without significant inflammation, noting that our case did not stain for MHC class I, which is seen upregulated in the majority of the muscle biopsies of this patient. Of note, though a thigh muscle MRI was not obtained in this patient, findings of extensive muscle oedema, atrophy and possible fatty replacement would be strongly suggestive of IMNM.[2]

Treatment of IMNM relies on targeting possible triggers, such as discontinuation of statins and high-dose immunosuppression. Optimal immunosuppression should be delivered in a stepwise approach of both glucocorticoids and glucocorticoid-sparing agents, with the addition of IVIG, rituximab and/or other biologics if responses are insufficient.[2] Tapering of immunosuppression must be performed carefully, as rates of relapse are high.[5] This patient's atorvastatin was not discontinued until several weeks after his initial presentation, which may have exacerbated his condition. In addition, after the correct diagnosis was made, he was treated with glucocorticoid monotherapy, which is often ineffective.[5] Under our care, he was successfully treated with triple therapy of glucocorticoids, mycophenolate mofetil and IVIG.

Most patients with IMNM experience improvement in muscle strength and CK levels,[5] both of which should be monitored—decreased CK levels do not necessarily indicate improvement and should therefore not be used as the sole sign of response to therapy.[2] Predictors of favourable outcome include the male sex, the use of two or more immunosuppressants in the first 3 months and early use of IVIG, all of which were fulfilled by this patient.[5]

Although IMNM is a rare condition, it is devastating to both patients and physicians. In this case, the patient's abrupt functional decline created significant physical, emotional and financial challenges, including the loss of independence, repeat hospitalisations, invasive procedures and need for prolonged physical therapy and rehabilitation. Early workup for an inflammatory myopathy and appropriate high-dose combination immunosuppression is critical. There is therefore a need for increased physician awareness of IMNM, its mechanism and optimal treatment to prevent such severe functional decline, as well as prospective studies on clinical outcomes and research trials for new therapies.

Learning points

- Immune-mediated necrotising myopathy (IMNM) is an inflammatory myopathy with the distinct clinicopathological features of subacute proximal muscle weakness, elevated creatine kinase (CK) levels and prominent myofibre necrosis and regeneration with little or no inflammation on muscle biopsy.
- While statins are the strongest risk factor for anti-HMG-CoA reductase (HMGCR)-associated IMNM, 30%–50% of patients have no history of statin exposure.
- Persistently elevated CK levels and proximal muscle weakness should prompt clinicians to obtain an early referral to rheumatology and send a complete workup for IMNM, which includes testing for antisignal recognition particle, antisynthetase and anti-HMGCR antibodies, as well as a proximal muscle MRI followed by muscle biopsy.
- It is critical to differentiate IMNM from severe rhabdomyolysis caused by statins since the pathophysiology, clinical presentation and treatment are markedly different.
- IMNM should be treated with appropriate combination immunosuppressive regimens as early as possible to prevent clinical deterioration and maximise chances of recovery.

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