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Case Report

Statin-induced immune mediated necrotising myopathy presenting with a markedly elevated cardiac troponin T in the absence of myocardial injury

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Abstract

Cardiac troponin (cTn) is a sensitive test to assess for myocardial injury. However certain clinical situations can result in a raised cTn in the absence of cardiac involvement. Here we present a case of a 65-year-old woman on long term atorvastatin who presented with generalised weakness, non-specific chest pain, and a persistently elevated high sensitivity cardiac troponin T. Upon further investigation acute myocardial injury was excluded and a diagnosis of statin-induced immune mediated necrotising myopathy (IMNM) was made. The patient improved with cessation of atorvastatin and initiation of immunosuppressive therapy with mycophenolate, intravenous immunoglobulin, and steroids. The mechanism for cTn elevation in skeletal myopathies without cardiac damage and the presentation and treatment of statin-induced IMNM are reviewed. We highlight the importance that in these cases the true cause of the raised cTn is recognised to allow prompt diagnosis and treatment of the underlying myopathy.

Keywords: statin-induced immune mediated necrotising myopathy; cardiac troponin

Introduction

Statin-induced immune mediated necrotising myopathy (IMNM) is a rare inflammatory myopathy estimated to effect 2–3 per 100 000 people treated with statins. Its clinical features include myalgia and bilateral proximal muscle weakness [1]. Statin-induced IMNM is associated with markedly raised creatinine kinase (CK), and cardiac troponin T (cTnT) can also be raised despite a lack of cardiac damage [2]. This latter finding can confuse the clinical picture and lead to a delay in diagnosis. Our case presented here highlights this point.

Case presentation

A 65-year-old woman was admitted with a one-month history of myalgia, generalised weakness, and intermittent non-specific chest pain.

She had suffered a stroke two years previously, which limited her mobility and for which she resided in a residential home. She had also experienced a non-ST elevation myocardial infarction (NSTEMI). with percutaneous coronary intervention to the left anterior descending artery five months prior to her current admission. Her other background included chronic kidney disease (CKD), dyslipidaemia, resistant hypertension, epilepsy, heart failure, type 2 diabetes mellitus, and asthma. She was a non-smoker and had no history of alcohol excess.

Her pre-admission medication included multiple antihypertensive medications, aspirin, ticagrelor, and insulin. She was also prescribed atorvastatin 80 mg ON, which she had taken for almost two decades, though the dose had been increased from 20 mg ON two years prior.

On examination she had globally reduced power more prominent on the right, which was the side affected by her previous stoke, and generalised muscle tenderness. The rest of the clinical examination was grossly unremarkable with a normal cardiovascular examination and no other evidence of an underlying rheumatological process such as a rash or joint swelling.

The most notable finding from her initial laboratory investigations was a markedly elevated high sensitivity cardiac troponin T (hs-cTnT) level of 3794 ng/l (normal < 12 ng/l), with no significant dynamic change between serial tests, and which was noted to have been raised at a similar level several months prior following her NSTEMI. A creatine kinase (CK) was subsequently checked which was also found to be significantly raised at 9416 U/l (normal 25-200 IU/l). Her other initial blood results are shown in Table 1.

Her ECG showed no acute changes (Fig. 1), and her transthoracic echocardiogram (TTE) showed left ventricular hypertrophy (LVH), but normal left ventricular ejection fraction without regional wall motion abnormalities, normal right ventricular function, and no significant valvular pathology.

It was initially unclear if her CK represented cardiac or skeletal muscle damage. The significance of the raised hs-cTnT was also

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Table 1. Inital blood results. Anaemia and raised creatinine are at patient's baseline. Note also the raised ALT, mildly raised CRP, and raised TSH with normal fT4.

Laboratory Test	Result	Reference Range and Units
Hb	81	115–165 g/l
WBC	12.6	4–11 x10^9/l
Creatinine	210	45–84 μmol/l
eGFR	26	>90 ml/min/1.73 m^2
CRP	20	<5 mg/l
ALT	169	5–33 U/l
ALP	44	30–130 iU/l
Albumin	31	35–50 g/l
Total Bilirubin	3	<21 μmol/l
TSH	6.25	0.30–4.20 mU/l
Free T4	20.5	12.0–22.0 pmol/l

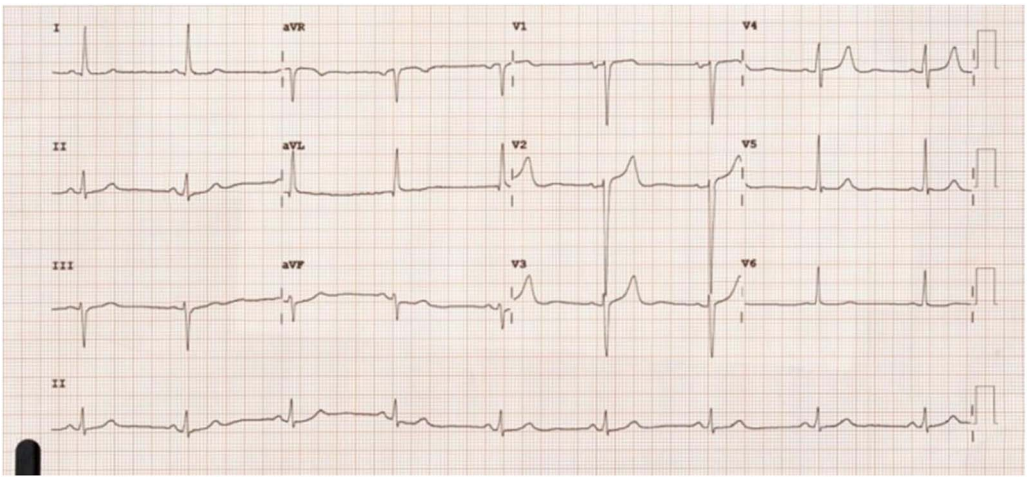

Figure 1. Initial 12-lead ECG showing mild sinus bradycardia, as well as large QRS amplitude and lateral T-wave flattening consistent with LVH. Appearances were similar to ECGs from previous admissions, and no dynamic changes were seen on serial ECGs.

uncertain. Acute coronary syndrome was thought to have been excluded as her initial presenting symptoms were inconsistent with this, there were no acute ECG or TTE changes, and the hs-cTnT levels were relatively static. The differential diagnosis was felt to be between chronic myocarditis, with the weakness being either due to co-existing myositis or deconditioning, and myositis without cardiac involvement and with a false hs-cTnT elevation.

Further tests were requested to differentiate between these two possibilities. A high sensitivity cardiac troponin I (hs-cTnI) was performed and was only mildly raised at 55 ng/l. A paired hs-cTnT taken at the same time remained significantly elevated at 4532 ng/l. A cardiac MRI showed no evidence of cardiac infiltration or inflammation. A focal area late gadolinium enhancement likely due to her previous NSTEMI was seen (Fig. 2).

Based on the above investigations significant acute cardiac injury was felt to have been excluded. Myositis with false hs-cTnT elevation was now considered the most likely diagnosis and a rheumatology opinion was sought. They advised a number of antibody tests. Of these HMG-CoA Reductase antibodies were positive and PM/SCL75 antibodies were weakly positive. Other additional recommended tests done at this time, including ANA, ANCA, and hepatitis B/C, were negative, and A CT thorax, abdomen, and pelvis showed no evidence of underlying malignancy. The initial finding of a raised TSH meant that hypothyroidism contributing to the myositis had to be considered. However the fT4 was found to be normal, indicating the patient had subclinical hypothyroidism and excluding this as a significant contributing factor.

A bilateral MRI of the thighs was also advised, which revealed diffuse high signal change throughout the thigh muscles with surrounding oedema in keeping with widespread myositis (Fig. 3).

Based on the clinical, MRI, and antibody findings a diagnosis of statin-induced IMNM was made. For confirmation a muscle biopsy from the quadriceps was taken. The results were not available until after discharge but when examined showed changes consistent with IMNM (Fig. 4).

Following diagnosis her atorvastatin was stopped and the patient was started on prednisolone 40 mg OD. However she had a modest response, with a reduction of her CK levels but little change to her symptoms. Therefore after two weeks of steroid treatment she was commenced on an escalating dose of mycophenolate starting at 250 mg BD and intravenous immunoglobulin 2 g/kg over five days alongside a three-day course of IV methylprednisolone 500 mg OD followed by an increased dose of oral prednisolone at 60 mg OD. This resulted in a progressive improvement of symptoms and continued reduction in her CK levels (Table 2). Her cTnT also decreased, but still remained significantly raised above her previous baseline, even after several months of treatment (Table 3). She was discharged home on mycophenolate (1 g BD at time of discharge) and a weaning dose of prednisolone (30 mg OD at time of discharge). She was planned for follow up under the rheumatology team but unfortunately repeatedly did not attend her scheduled clinic appointments.

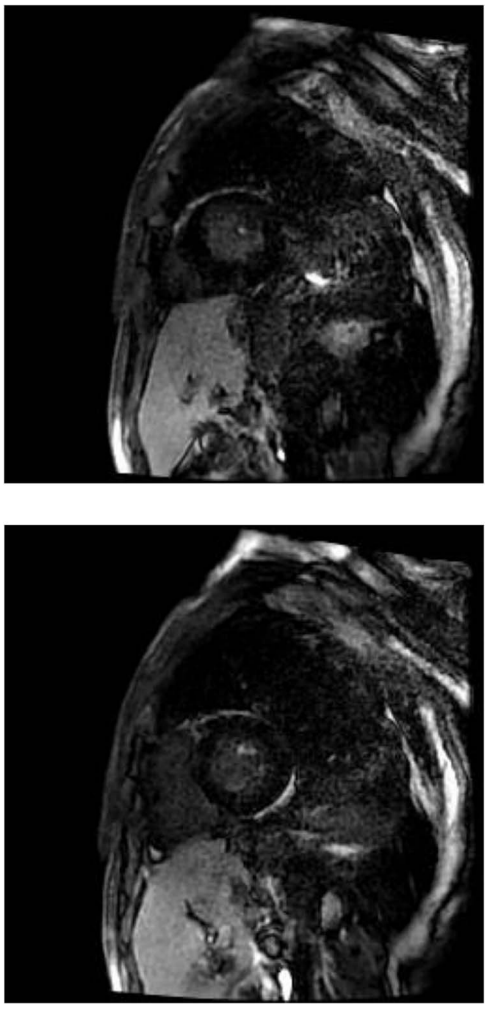

Figure 2. Short axis images from patient's cardiac MRI showing an area of late gadolinium enhancement of the anterolateral papillary muscle, which likely represents scarring caused by her previous NSTEMI.

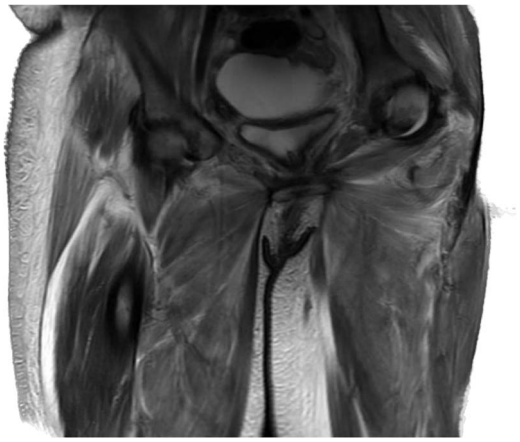

Figure 3. Coronal image from an MRI of the thighs showing widespread high signal change and oedema throughout the musculature consistent with diffuse myositis.

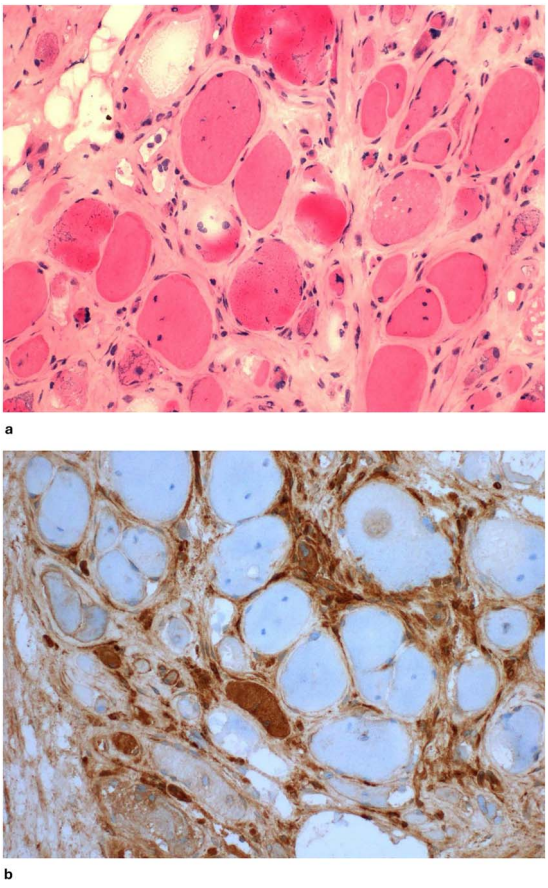

Figure 4. Histology slides from quadriceps muscle biopsy. Figure 4a (stained with hematoxylin and eosin) demonstrates marked variation in fibre size and fibre necrosis, along with an increased number of internalised myonuclei and some fibre splitting. There is minimal evidence of inflammation but marked endomysial fibrosis. Figure 4b (immunohistochemical staining for MHC class 1 (HLA ABC) has been applied) shows expression of MHC class 1 on the sarcolemma. Combined these findings are consistent with statin-induced immune mediated necrotising myopathy with a degree of chronicity.

Discussion

Under normal circumstances cTn is only found in cardiac myocytes and therefore raised levels are usually reliable indicators of cardiac injury. However in pathology resulting in muscle damage, such as myositis, cTn is often found to be raised in the absence of myocardial injury. Specifically skeletal myopathies have been found to cause cTnT to be elevated far more frequently than cTnI [3]. Previous false positive raised cTnT with statin-induced IMNM specifically has also previously been described [2].

Two major competing theories exist to explain these findings; Firstly, muscle damage may result in release of skeletal TnT which cross reacts with cTnT assays causing a false reading of cTnT elevation. Conversely skeletal TnI seemingly does not cross react with cTnI as readily [4]. Secondly, it may be that myopathy induced muscle damage results in the regenerating muscle re-expressing cTnT, but not cTnI [5]. In this case the cTnT are truly elevated but the source is not cardiac. In both cases in the absence of co-existing myocardial damage cTnI levels should be normal. Other non-myopathy causes of non-cardiac cTn elevation also usually produce a significant discrepancy between cTnT and cTnI, though the mechanisms differ and some causes, such as the presence of circulating macrotroponin complexes, can cause cTnI to be raised more commonly than cTnT [6]. Therefore if a non-cardiac cause for raised cTn is suspected paired testing of cTnT and cTnI is useful. In our case the cTnT was far higher than the cTnI, and while the cTnI levels were not normal, the modest raise above the

Table 2. CK results trend (reference range 25-200 IU/l).

22/06/23 (Inital result)	27/06/23 (prior to starting oral prednisone)	10/07/23 (prior to starting IV methylprednisolone)	14/07/23 (started on IVIG and mycophenolate)	28/07/23	15/08/23 (result at time of discharge)	04/10/23
9416	7702	2882	2364	1711	1307	611

Table 3. hs-cTnT results trend (reference range < 12 ng/l).

26/09/22 (previous baseline)	15/01/23 (peak troponin during admission with NSTEMI)	25/03/23 (first significantly raised result)	14/06/23 (initial result for current admission)	24/06/23 (prior to starting oral prednisolone)	18/08/23 (result at time of discharge)	28/10/23
57	357	2798	3794	4532	1549	965

upper limit of normal was likely due to the patient's CKD and LVH, both of which are known to commonly produce chronic troponin elevations in the absence of acute myocardial damage.

The patient was diagnosed with statin-induced IMNM after been found to have widespread muscle inflammation on an MRI of the thighs, and have positive antibodies against HMG-CoA, which is highly sensitive for IMNM [1]. PM/SCL75 antibodies were also found to be positive and are associated with a number of autoimmune conditions included myositis [7].

Statin-induced IMNM often occurs after years of statin use [1], as was the case in our patient, and the lack of a clear temporal association has the potential to contribute to a delay in diagnosis. Stopping the statin alone rarely results in improvement and long term immunosuppressants need to be initiated to maximise the chance of muscle recovery [8]. As demonstrated with our patient steroids alone are often insufficient, and combined treatment is often necessary; A previous case review showed that 84% of patients required use of two or more immunosuppressive agents, but that remission was able to be induced in 91% of patients [9].

Even once myositis has been confirmed it is important to ensure active myocardial pathologies, such as myocarditis, have been excluded, as these can present concurrently [10]. As well as ECG and TTE, cardiac MRI is particularly useful in these situations. In select cases CT or invasive coronary angiography may also be indicated.

In conclusion we present a case where the rarity of statin-induced IMNM combined with the patient's complex background and unexpected markedly raised cTnT level led to diagnostic difficulty. Clinicians should be aware of this condition as a cause of raised cTnT without cardiac injury.

Consent

Written informed consent was obtained from the patient.

Guarantor

David Hall.

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Conflict of interest

No conflicts of interest.

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Ethical approval

Not required.

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