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Chest Pain, Statins, Troponin Elevation, and Myopathy: A Diagnostic and Management Dilemma

Daniel T. Tardo, MBBS,[a,b,c] Alana Bruce, MBBS,[d,e,f] Alice Pearlman, BMedBSc,[g] Louis W. Wang, MBBS, MM, PhD,[a,h] Allan Sturgess, MBBS, PhD,[d,h] Mark Pitney, MBBS[h,i,j]

[a]*Department of Medicine, St Vincent's Hospital, Darlinghurst, NSW, Australia;* [b]*School of Medicine, University of Notre Dame Australia, Sydney, NSW, Australia;* [c]*Victor Chang Cardiac Research Institute, Darlinghurst, NSW, Australia;* [d]*Department of Rheumatology, St George Hospital, Kogarah, NSW, Australia;* [e]*Department of Rheumatology, Campbelltown and Camden Hospitals, Campbelltown, NSW, Australia;* [f]*School of Medicine, Macquarie University, Sydney, NSW, Australia;* [g]*Royal Prince Alfred Hospital, Camperdown, NSW, Australia;* [h]*School of Medicine, University of New South Wales, Kensington, NSW, Australia;* [i]*Department of Cardiology, Sutherland Hospital, Caringbah, NSW, Australia;* [j]*Department of Cardiology, Prince of Wales Hospital, Sydney, Australia.*

PRESENTATION

A 64-year-old man with known ischemic heart disease and previous myocardial infarction and stent implantation presented to the Emergency Department with bilateral arm pain and chest discomfort with mixed features. He described a dull, central sensation within the chest, which did not radiate to the neck, jaw, or back. Additionally, he had a 3-week history of fatigue and intermittent myalgias, predominantly affecting the shoulders on exertion. Cardiac risk factors included hypertension and hypercholesterolemia. There was no history of diabetes mellitus, with normal baseline renal function (creatinine 80 μmol/L, estimated glomerular filtration rate >90 mL/min/1.73 m^2). Regular medications included atorvastatin, olmesartan, hydrochlorothiazide, spironolactone, and allopurinol. He was known to have mild left ventricular dysfunction with a previous transthoracic echocardiogram showing an ejection fraction of 45%. The patient has been on long-term statin therapy, but 3 weeks prior to presentation, atorvastatin 40 mg had been changed to rosuvastatin 20 mg and symptoms had begun at that time.

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Requests for reprints should be addressed to Daniel T. Tardo, MBBS, Department of Medicine, St Vincent's Hospital, 390 Victoria Street, Darlinghurst, Sydney, NSW 2010, Australia.

E-mail address: daniel.tardo1@my.nd.edu.au

ASSESSMENT

Cardiovascular examination revealed a regular heart rate of 80 beats per minute, blood pressure of 135/70 mm Hg, and no clinical signs of left or right heart failure. Electrocardiogram (ECG) showed inferior Q waves, which were preexisting. Musculoskeletal examination demonstrated difficulty standing from a chair and proximal muscle weakness of the shoulder girdle and neck (4/5 power in all proximal muscle groups, with preserved distal power).

Cardiac troponin T (cTnT) were 889 ng/L on admission, and 4 hours later, 808 ng/L (<14 ng/L). Urgent transthoracic echocardiography demonstrated normal left ventricular size with mild segmental left ventricular dysfunction (inferior septal, posterior and inferior akinesis, mid-posterior hypokinesis) consistent with previous inferior myocardial infarction, which was present on prior echocardiograph. A cTnT level 12 hours post admission was relatively stable, reaching 953 ng/L in the absence of any further chest pain, and no arrhythmias were detected on telemetry.

DIAGNOSIS

The initial differential diagnosis included an acute coronary syndrome with co-existing toxic statin myopathy or statin-related necrotizing autoimmune myopathy, or other systemic myopathy with cardiac involvement. Other possibilities, such as false-positive troponins secondary to heterophile antibodies, were considered.

An early myocardial perfusion scan showed evidence of old inferoposterior infarction but no ischemia, and given the atypical troponin pattern (static elevation), and absence of new ECG or echocardiographic changes with atypical pain, an acute coronary syndrome was considered unlikely.

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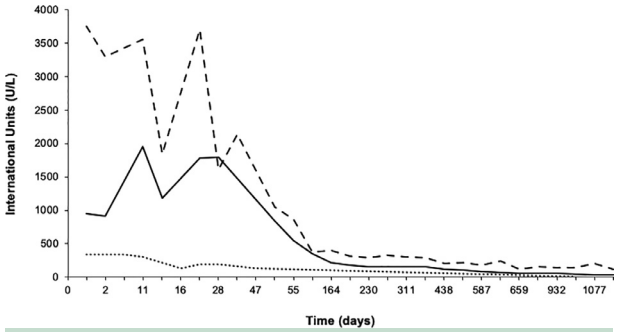

Figure 1 Trend in biomarkers from the time of presentation (day 1) through to follow-up to date, at 3.5 years (day 1165). Creatine kinase (dashed line), cardiac troponin T (solid line), and cardiac troponin I (dotted lined).

Creatine kinase (CK) was significantly elevated at 3752 U/L (<70 U/L) with abnormal aminotransferases (aspartate aminotransferase 173 U/L and alanine aminotransferase 108 U/L), but with normal gamma-glutamyl transferase (29 U/L) and alkaline phosphatase (72 U/L) (Figure 1). A working diagnosis of a toxic myopathic process possibly caused by the recent change in statin was made. Subsequently, anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase antibody was negative, making statin-induced necrotizing autoimmune myopathy unlikely. The troponin elevation, which persisted, would not be explained by necrotizing autoimmune myopathy or a toxic statin myopathy (Figure 1).

Electromyography confirmed a myopathic process with a degree of necrosis of his deltoid and quadriceps. An alternate troponin assay, cardiac troponin I (cTnI), was performed and remained elevated at 346 ng/L (0-10 ng/L). A cardiac magnetic resonance imaging scan was performed and showed evidence of an old inferior infarct, but no evidence of active cardiomyopathy, infiltrative disease, or myocarditis.

Further blood tests showed a strongly positive antinuclear antibody (1:5,120) and positive anti-Mi2 antibody. It was decided to proceed with a muscle biopsy of the left vastus lateralis; this showed necrotic and regenerating myofibers with focal major histocompatibility complex class I upregulation and a lack of inflammatory infiltrates consistent with necrotizing autoimmune myositis (Figure 2).

While these investigations were being performed, the patient's clinical condition progressed, with worsening proximal weakness of the upper and lower limbs, reduced upper limb reflexes, dysphagia, facial plethora without nasolabial fold sparing, erythematous lesions over the proximal interphalangeal, distal interphalangeal and metacarpophalangeal joints of the hands; and new weakness of the cervical spine, hip, and shoulder girdle muscles.

Given the clinical findings, muscle biopsy result, markedly elevated CK and anti-Mi2 antibody, and negative anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase antibody, a final diagnosis of dermatomyositis was made.

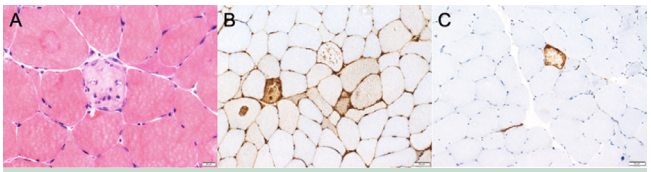

Figure 2 Vastus lateralis muscle biopsy. Hematoxylin and eosin (H&E)-stained paraffin sections of type I and II myofibrils showing no abnormalities in fascicular architecture, myofiber nuclear position, or cytoplasmic contents, and no evidence of perifascicular atrophy, or endomysial or perivascular inflammation **(A)**. Major histocompatibility complex class I (MHC1) staining demonstrating upregulation of scattered necrotic myofibers **(B)**. Membrane attack complex (MAC) staining revealing scattered atrophic myofibrils and one capillary, scattered atrophic myofibers, polyclonal and angular, of both myofiber types, a few being esterase positive **(C)**. This pattern of necrotizing autoimmune myopathy is most frequent with anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase and anti- signal recognition protein antibodies, but can occur in other autoimmune myopathies including Mi2-associated dermatomyositis.

MANAGEMENT

Rosuvastatin was ceased on admission. Following electromyography and muscle biopsy, the patient was commenced on 60 mg prednisolone daily, which resulted in gradual improvement in lower limb power.

The ongoing troponin (both cTnT and cTnI) elevation caused clinical concern. In view of a negative cardiac magnetic resonance imaging scan, the raised troponin was thought to be a false-positive result, as this is known to occur frequently. Schmid et al[1] assessed cardiac troponin elevations in patients with varied genetic or acquired skeletal myopathies in the absence of cardiac disease and found that cTnT concentrations were chronically elevated in most patients, likely due to cross-reactivity of the cTnT immunoassay with skeletal muscle troponin isoforms, while cTnI elevation rarely occurred.[1] Proposed mechanisms include re-expression of cardiac isoforms in diseased skeletal muscle and cross-reactivity of cardiac troponin assays with other troponin isoforms.[1,2]

Although a false-positive troponin was likely, subclinical myocarditis could not be excluded, especially as cTnI was elevated. Cardiac involvement in polymyositis and dermatomyositis can occur as a rare extramuscular manifestation, caused by the same autoimmune inflammatory process affecting skeletal muscle.[3,4] Subclinical manifestations, namely conduction abnormalities, are more common than overt symptomatic heart disease observed in more severe disease states such as necrotizing autoimmune myositis[3-5] (Table).

Symptoms may be present at the time of diagnosing myositis or develop progressively, even after commencing immunotherapy.[4] Cardiac manifestations are among the most common cause of mortality in myositis patients secondary to heart failure, arrhythmias, myocardial infarction, and cardiac arrest.[4,6,7,8] Myocarditis is a well-recognized

Table Cardiac Manifestations and Electrocardiogram Changes in Inflammatory Myopathies

Cardiac Involvement	Clinical Findings
Clinical manifestations	• Heart failure with reduced ejection fraction • Heart failure with preserved ejection fraction • Coronary artery disease • Acute coronary syndrome • Coronary vasospasm (Prinzmetal angina) • Myocarditis • Coronary vasculitis • Vascular hyperplasia
Subclinical manifestations	• Conduction abnormalities and arrhythmia
Electrocardiogram findings	• Atrial arrhythmia • Ventricular arrhythmia • PR prolongation • AV block • High-grade heart block • Bundle branch blocks • QT prolongation • Ventricular ectopic beats • Abnormal Q waves • Nonspecific ST-segment and T-wave changes

AV = atrioventricular.

complication of dermatomyositis, particularly with anti-signal recognition protein antibodies but also described with anti-Mi2.[4,9,10] Recently, there have been increasing reports of dermatomyositis apparently induced by the use of statins. Spiro and Butts[11] described a case very similar to ours in which atorvastatin use was associated with dermatomyositis and anti-Mi2 antibodies.

The patient was initially treated in the coronary care unit, followed by ongoing cardiac observation with daily ECGs prior to discharge. Frequent outpatient cardiac reviews were scheduled, including serial echocardiography looking for progressive left ventricular dysfunction. Cardiac biopsy and positron electron tomography scanning were considered, but it was felt that they would not change management.

Despite an initial improvement on steroids, the patient's myopathy progressed with proximal and axial muscle weakness limiting his function, and he was commenced on intravenous immunoglobulin. The CK was persistently elevated to 1700 U/L. Following 4 doses of intravenous immunoglobulin, an acute kidney injury developed, with serum creatinine rising to 150 μmol/L, thought secondary to that treatment, and the patient was transitioned to methotrexate as a steroid-sparing agent in addition to ceasing his angiotensin-receptor blocker.

During subsequent reviews by the cardiologist, left ventricular function remained unchanged, but troponin remained persistently elevated. Approximately 1 year following his initial presentation he complained of increasing shortness of breath. A repeat stress test was strongly positive, and coronary angiography showed high-grade lesions in the left anterior descending and circumflex arteries, but with normal flow. These lesions were corrected with drug-eluting stents; his stress test returned to normal but troponin remained persistently elevated for a further 12 months, after which time CK and troponin normalized.

Currently he is asymptomatic, but remains on methotrexate some 3 years post presentation, with normal muscle strength and no evidence of ischemia on cardiac stress testing. The diagnosis of dermatomyositis seems clear; the exact cause for troponin elevation remains controversial.

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