

Differential Expression of Cardiac Troponin T and I in a Patient with Isolated Skeletal Muscular Sarcoidosis

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Abstract

A 49-year-old female was referred to our hospital due to high serum creatine kinase (CK) (2,605 IU/L) and serum cardiac troponin T (cTnT) (0.342 ng/mL) levels. She had no other complaints and further examinations suggested no signs of cardiac disease. Additionally, the serum cardiac troponin I (cTnI) levels were normal. She reported having gradually felt difficulty in walking upstairs. A biopsy indicated skeletal muscle sarcoidosis with positive staining for cTnT. Steroid therapy immediately resolved her muscular symptoms with a normalization of the serum CK levels. Since the serum levels of cTnI were normal, the concomitant measurement of cTnT/cTnI might be useful to diagnose skeletal muscular disease biochemically in such cases.

Key words: cardiac troponin T, cardiac troponin I, sarcoidosis, skeletal muscle

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Introduction

Sarcoidosis is an inflammatory disease characterized by the presence of noncaseating granulomas in multiple organs, including the lung, skin, eye, liver, and heart (1). Although muscular involvement is relatively common, isolated skeletal muscular sarcoidosis is reported to be rare (2). Both cardiac troponin T (cTnT) and I (cTnI) are specific markers of cardiac injury (3). Recent papers, however, have demonstrated that cTnT is induced in diseased skeletal muscle with Becker muscular dystrophy, Duchenne muscular dystrophy, Friedreich's ataxia, inclusion body myositis, limb girdle muscular dystrophy, myasthenia gravis and myotonic dystrophy (4, 5). In the present paper, we report a case of sarcoidosis with the induction of cTnT in the diseased skeletal muscle without any involvement of the heart. Because several samplings of serum cTnI were within the normal ranges in this case, the concomitant measurement of cTnT and cTnI

might therefore be useful to diagnose skeletal muscular sarcoidosis biochemically in such cases.

Case Report

A 49-year-old female was referred to our hospital due to high levels of serum creatine kinase (CK) (2,605 IU/L; normal range: 41-153). She had been treated with ferric medicine for anemia due to uterine fibroids. She had no episodes of chest discomfort, and her electrocardiogram and echocardiogram findings revealed no abnormalities. Although her serum levels of cTnT were elevated (0.342 ng/mL; normal range <0.014), as confirmed by two independent assays, the CK-MB and cTnI levels were within the normal limits without any renal dysfunction, hypothyroidism or other specific findings. Computed tomography and magnetic resonance imaging showed no evidence of either coronary arterial lesions, myocardial injury or skeletal muscle injury.

Twenty weeks after her first visit, she gradually began to

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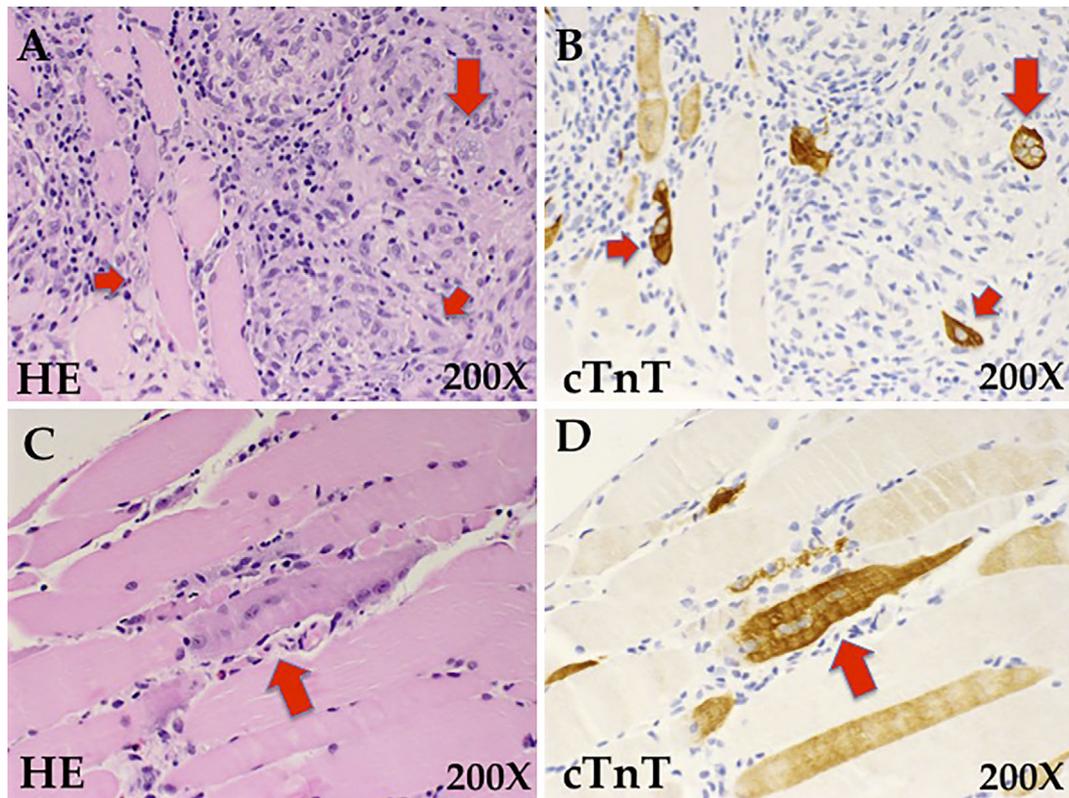


Figure 1. Histological examination of biopsied skeletal muscle samples. Immunohistochemistry procedures were performed with an established method using formalin-fixed, paraffin-embedded sections. The following antibodies were used and diluted as shown: Cardiac troponin T (cTnT), Cardiac Isoform Ab-1 (Lab Vision Corp., Fremont, USA, Cat. no. # MS-295-P1; 1: 100). To detect bound antibodies, slides were incubated with antimouse-labeled polymer peroxidase and developed with the HRP/ DAB Detection System [Horseradish peroxidase/Diaminobenzidine (Dako)] for 2 min. Skeletal myocytes in noncaseating granulomas stained positive for cTnT (arrows) (A, B), as well as a skeletal myocyte surrounded by inflammatory cells (C, D).

feel difficulty in walking upstairs. Her manual muscle test (MMT) score was 4/5 in the proximal limb muscles at this time. An electromyogram on her right bicep showed low voltage and short duration motor unit potentials. Therefore, a biopsy of her bicep was performed and revealed non-caseating epithelioid granuloma (Fig. 1A), suggesting sarcoidosis. Immunohistochemical staining for cTnT was positive in the degenerated skeletal muscle (Fig. 1B and D). No evidence of lung, eye or skin lesions was observed by routine physical and radiographic examinations. Contrast cardiac MRI showed no abnormality in the heart. Whole body positron emission tomography using fluorodeoxyglucose (FDG-PET) detected an uptake only in the gastrocnemius muscles and no abnormal uptake in the heart or any other organs. The serum levels of soluble interleukin-2 receptors were slightly elevated, while the angiotensin-converting enzyme (ACE) activity and lysozyme levels were within the normal limits. Because the patient exhibited symptoms of weakened skeletal muscle and abnormal histological findings, after excluding other types of skeletal muscle diseases, she was finally diagnosed with isolated skeletal muscular sarcoidosis, chronic myopathy type.

Her muscular weakness was accompanied by progres-

sively increasing CK (5,372 IU/L) and cTnT (0.45 ng/mL; Roche, Mannheim, Germany) levels. Therefore, steroid pulse therapy (intravenous methylprednisolone 1,000 mg/day for 3 days) was administered twice, followed by oral prednisolone (40 mg/day) two weeks later with gradual tapering. Her muscular symptoms subsequently improved, and the CK (131 IU/L) and cTnT (0.026 ng/mL; Roche) levels also normalized (Fig. 2).

Discussion

In the present case, the diagnosis of sarcoidosis was histologically established based on the presence of noncaseating granulomas in the biopsied skeletal muscle. No evidence of any cardiac involvement was demonstrated by electrocardiogram, echocardiography, cardiac CT, cardiac contrast MRI, or FDG-PET examinations. Because further examination revealed no sarcoidosis lesions in the lung, skin, eye or liver, the patient was diagnosed with isolated skeletal muscular sarcoidosis.

The elevation of the serum cTnT levels was confirmed by two independent assays in the present patient. The value of cTnT was 0.257 IU/L according to an electrochemilumines-

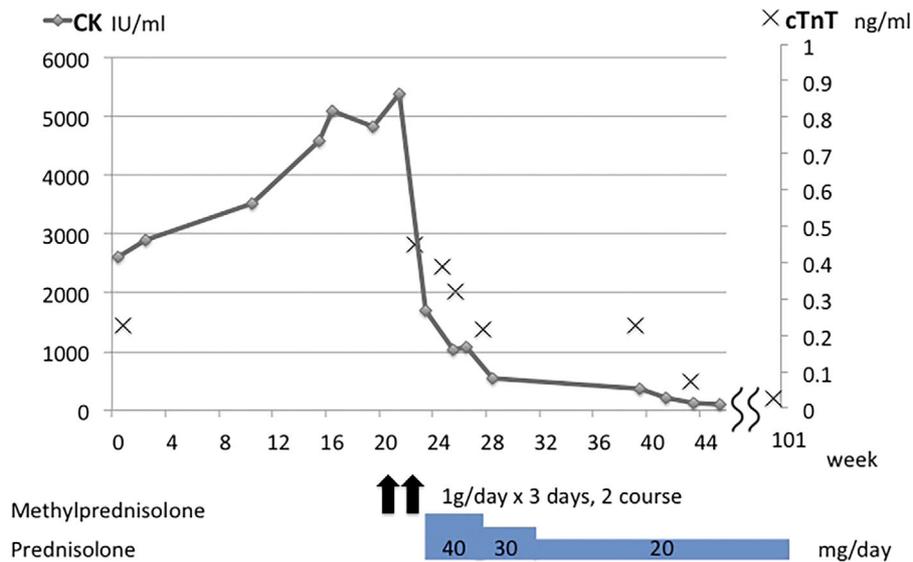


Figure 2. Time course of creatine kinase (CK) and cardiac troponin T (cTnT) in response to steroid therapy.

cence immunoassay (Roche) and 0.342 IU/L based on a chemiluminescent enzyme immunoassay (Wako, Osaka, Japan), both of which were more than 18 times higher than the normal upper limit (<0.014 IU/L). However, the serum levels of cTnI were not elevated (0.051 IU/L <0.06, Siemens Healthcare, Japan). Due to the fact that cTnI has been shown to be a more sensitive marker of myocardial injury than cTnT (6), the absence of cTnI elevation suggested that the elevated levels of serum cTnT were not the result of myocardial damage.

Four isoforms of cTnT derived from alternative splicing are known to be expressed in cardiac muscle in a developmentally regulated manner (7). cTnT isoforms have also been shown to be expressed in fetal human skeletal muscle, while they are downregulated after birth, leading to the absence of cTnT in healthy adult skeletal muscle (7). Recent studies have demonstrated that cTnT is reexpressed in diseased skeletal muscle (5). Therefore, the reexpression of cTnT might be a common process observed in regenerating skeletal muscle after injury. In contrast, cTnI has not been shown to be expressed in skeletal muscle at any point during development (8). In the present case, cTnI was also negative, despite high levels of cTnT, suggesting that the concomitant measurement of cTnT and cTnI could therefore distinguish skeletal muscle injury from myocardial damage.

In conclusion, we experienced a case of isolated skeletal muscular sarcoidosis with the induction of cTnT without any involvement of the heart. To the best of our knowledge, this is the first report of isolated skeletal muscular sarcoidosis associated with elevated serum cTnT levels and the histological documentation of cTnT. Because the serum levels of cTnI are often normal in patients presenting with skeletal muscle disease, the concomitant measurement of cTnT and

cTnI might therefore be useful to discriminate cardiac and muscular diseases biochemically.

The authors state that they have no Conflict of Interest (COI).

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