Takotsubo Cardiomyopathy with Involvement of Delayed-onset Rhabdomyolysis and Acute Kidney Injury after Rosuvastatin Treatment

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Abstract

Takotsubo cardiomyopathy is a disorder characterized by left ventricular apical ballooning with preceding emotional and/or physical stressors. This condition is also an important differential diagnosis of acute coronary syndrome. We herein describe a case of Takotsubo cardiomyopathy, a significant clinical phenomenon, triggered by delayed-onset rhabdomyolysis following the administration of long-term statin treatment, without any preceding stressors or changes in the patient’s medical condition, in association with complaints of non-specific muscle-related symptoms. Although an electrocardiogram showed remarkable ST-segment elevation, a careful reading of the electrocardiogram findings revealed the features of Takotsubo cardiomyopathy. Withdrawing the statin therapy improved the patient’s cardiac function.

Key words: Takotsubo cardiomyopathy, statin, rhabdomyolysis, ST elevated myocardial infarction (STEMI)

(DOI: 10.2169/internalmedicine.54.3239)

Introduction

Although the mechanism(s) underlying the development of Takotsubo cardiomyopathy, which is associated with left ventricular apical ballooning, have not been established, this reversible disorder is known to be triggered by intense emotional or physical stress. Several cases thought to have been induced by the adverse effects of drugs have been reported; however, the onset of disease occurred in the early period of therapy in most cases.

Case Report

A 73-year-old man presented to our hospital complaining of acute-onset general fatigue and dysbasia with inferior limb adynamia. The cause of his symptoms was unclear, and we considered the possibility of infection, injury or other mental and/or physiological stressors. The patient had a medical history of dyslipidemia, diabetes mellitus and arteriosclerosis obliterans, and his current medications included rosuvastatin (2.5 mg), glimepiride (3 mg), miglitol (150 mg), pioglitazone hydrochloride (15 mg), limaprost alfadex (15 μg) and cilostazol (100 mg). With the exception of the addition of miglitol two years earlier, the drug regimen had remained unchanged for four years. Additionally, no temporary administration of other agents, including fibrates, was performed for at least six months. Although the patient had a history of bilateral aorta-femoral artery bypass approximately 12 years earlier, there was no current information regarding his coronary circulation. In addition, there were no specific findings in his family history.

The patient’s consciousness was clear, and his main vital signs were almost within the normal limits, including his blood pressure, pulse rate and body temperature. His muscle strength was decreased in the bilateral inferior limbs; how-
ever, there were no sensory abnormalities or muscle tenderness.

Blood tests performed at presentation showed renal dysfunction, with a serum creatinine level of 1.4 mg/dL (baseline: 0.5 mg/dL) and markedly elevated creatine kinase (CK) level of 16,538 U/L, although the CK-MB level was 35 U/L. A delayed analysis of the CK isozyme revealed that 96% of the increased CK was of the MM form. Other representative data are shown in Table. An electrocardiogram (ECG) demonstrated remarkable ST-segment elevation in the I, II, aVF, aVL and V2-6 leads in addition to ST-segment depression in the aVR lead (Fig. 1A), without chest pain, dyspnea or any other cardiac symptoms. The patient’s ECG findings and symptoms remained unaltered despite the intravenous administration of isosorbide dinitrate. Echocardiography disclosed left ventricular apical akinesia and a global reduction in left ventricular contractions; the ejection fraction measured according to Simpson’s method was 52%. No other critically severe findings, such as valvular disease or left ventricular outflow tract obstruction, were detected.

After admission, the withdrawal of rosuvastatin therapy and the administration of intravenous fluids improved the CK and creatinine levels. On the third hospital day, cardiac catheterization was performed after the patient’s renal function had recovered. Although left ventriculography showed extensive akinesis limited to the apical segments, with hyperkinesis in the basal segments (Fig. 2), coronary angiography showed no critical stenosis or occlusion (Fig. 3), despite the prolongation of ST elevation on ECG. Simultaneously, ergonovine-induced coronary vasospasms were challenged, with negative results. Based on these findings, the patient was diagnosed with Takotsubo cardiomyopathy.

A subsequent serial ECG revealed sustained ST-segment elevation on the third hospital day (Fig. 1B), followed by ST-segment resolution in the lead with previous ST-segment elevation on the fifth hospital day (Fig. 1C) and T-wave inversion in the same leads as on admission on the tenth hospital day (Fig. 1D). Finally, the ECG findings on the 31st day showed sustained negative T-waves in the same leads. Following the prolongation of LV apical ballooning for a few days (Fig. 4), an echocardiographic evaluation demonstrated a gradual reduction in the area of LV ballooning. Meanwhile, the left ventricular ejection fraction recovered to 62% on the seventh hospital day, then to 65% on the 18th hospital day.

Prior to the patient’s hospital discharge on the 20th hospital day, blood tests revealed normalization of his renal function and CK level.

### Discussion

Usually seen in postmenopausal women, the clinical presentation of Takotsubo cardiomyopathy is similar to that of acute coronary syndrome with ECG abnormalities. The ECG findings at presentation vary in patients with Takotsubo cardiomyopathy and can include ST-T wave changes. ST-segment elevation is detected in approximately one-third of patients, with the anterior leads being most commonly involved (1, 2). Although it has been reported that, in cases of anterior ST-elevation, the magnitude of the ST shift is usually less in patients with Takotsubo cardiomyopathy than in those with ST elevated myocardial infarction (STEMI), the ECG in the present case showed a remarkable rise in the ST segment (1). 12-lead ECG by itself is insufficient to differentiate Takotsubo cardiomyopathy from STEMI (3). However, distinguishing Takotsubo cardiomyopathy from STEMI based on ECG findings is essential for selecting the appropriate treatment strategy, including surgery with urgent coronary angiography at the early stage. Kosuge et al. (4) reported the utility of detecting ST-segment changes in the aVR lead for making the differential diagnosis between Takotsubo cardiomyopathy and anterior wall STEMI. The combination of the presence of ST-segment depression in the aVR lead and the absence of ST-segment elevation in the V1 lead can be used to diagnose Takotsubo cardiomyopathy with 91% sensitivity, 96% specificity and 95% accuracy, thus accurately differentiating Takotsubo cardiomyopathy from anterior wall STEMI. Notably, these ECG features of Takotsubo cardiomyopathy were found in the present case (Fig. 1, left▲). In addition, as the late blood test indicated an acute renal disorder, deferring coronary angiography was favorable as a renoprotective strategy.

Although the unique feature of Takotsubo cardiomyopathy is the occurrence of a preceding stressful emotional or
A: The initial ECG findings demonstrated remarkable ST-segment elevation in the I, II, aVF, aVL and V2-6 leads and slight ST-segment depression in the aVR lead. ▲: Takotsubo ECG changes in the aVR and V1 leads, which can be used to differentiate this condition from STEMI. B: ECG findings of sustained ST-segment elevation on the third hospital day. C: ECG findings of ST-segment resolution in the previously elevated leads on the fifth hospital day. D: ECG findings of T-wave inversion in the same leads on the 10th hospital day.

Figure 2. Left ventriculography findings of extensive akinesia limited to the apical segments with hyperkinesis in the basal segments.

physical event, no clear precipitating factor is identified in some patients. In the present case, the physiological stress of rhabdomyolysis may have induced Takotsubo cardiomyopathy, as the patient reported no emotional stress, de-
spite careful history taking by the clinicians. Rhabdomyolysis is the most severe adverse effect of statins and may result in acute renal failure. Post-marketing surveillance by the FDA has documented a rate of fatal rhabdomyolysis of 0.15 per 1 million statin prescriptions (5). The majority of cases of statin-induced rhabdomyolysis are related to a high dose of statins and the presence of drug interactions, primarily with fibrates (5, 6). Only one case report of Takotsubo cardiomyopathy complicated by rhabdomyolysis after combined treatment with rosuvastatin and fenofibrate has been published (7).

Furthermore, only a few papers have been published regarding the onset of statin-induced adverse reactions. In the PRIMO study, patients developed muscle symptoms after a median of one month (range: up to 12 months) after the initiation of statin therapy (8). Commonly reported predictors of myopathy include a history of muscle pain during previous lipid-lowering treatment, unexplained muscle cramps, previous CK elevation, a family history of muscle symptoms and hypothyroidism. Additionally, the administration of statin treatment for more than three months is associated with a reduced risk of myopathy (8). Importantly, the present patient had no risk factors for myopathy and consequently experienced a rare incident more than four years after taking a low dose of statins, without any typical drug interactions. Therefore, clinicians should be aware of the possibility of late-onset rhabdomyolysis in patients taking statins and that rhabdomyolysis may be a precipitating factor for the development of Takotsubo cardiomyopathy.

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

References

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