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Case Report

Coronary spastic angina in a multiple myeloma patient treated with bortezomib, lenalidomide, and dexamethasone

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ABSTRACT

Adverse cardiovascular events have been reported in patients with multiple myeloma. We present a case of coronary spastic angina during combination therapy with bortezomib, lenalidomide, and dexamethasone for multiple myeloma. A 70-year-old man, newly diagnosed with multiple myeloma, was admitted to our hospital at his fifth therapy cycle due to exertional chest pain. Coronary angiography revealed diffuse spasm in the left coronary artery, which normalized after intracoronary injection of nitroglycerin. Calcium channel blockers were effective in treating his coronary spastic angina and the patient resumed treatment for multiple myeloma. This case highlights the importance of being aware of the possibility of coronary spastic angina when combination therapy with bortezomib, lenalidomide, and dexamethasone is initiated.

<**Learning objective:** Combination therapy with bortezomib, lenalidomide, and dexamethasone has improved overall survival of multiple myeloma patients. However, these drugs can induce coronary spastic angina. Calcium channel blockers may be effective for coronary spastic angina and allow patients to continue multiple myeloma treatment.>

Introduction

Patients with multiple myeloma are often exposed to combination therapy with proteasome inhibitors (e.g., bortezomib), immunomodulators (e.g., lenalidomide), and dexamethasone. Although these drugs have been shown to improve overall survival, adverse cardiovascular events, such as congestive heart failure and venous thromboembolism, have been reported in multiple myeloma patients treated with these drugs [1].

Here, we describe coronary spastic angina during the treatment of multiple myeloma with bortezomib, lenalidomide, and dexamethasone.

Case presentation

The patient was a 70-year-old man who was newly diagnosed with multiple myeloma. He had no coronary risk factors, including smoking. Although he was a social drinker without alcohol flush reaction, he stopped drinking after the diagnosis of multiple myeloma. He underwent combination chemotherapy with bortezomib (1.3 mg/m^2 on days 1, 4, 8, and 11), lenalidomide (20 mg/day on days 1–14), and dexamethasone with a recycling period of 3 weeks (BLD therapy). During the sixth day of the fifth cycle of BLD therapy, he was admitted to our hospital due to exertional chest pain that occurred when he climbed stairs. The chest pain was relieved by rest. He experienced such chest pain three times in 24 h before admission. He was found to have an elevated serum Troponin I of 0.065 ng/mL (normal: <0.026 ng/mL), and biphasic T waves in precordial electrocardiogram (ECG) leads (Fig. 1). Therefore, we performed emergency coronary angiography (CAG). CAG revealed diffuse spasm in the left coronary artery, especially in the left anterior descending artery, which normalized after intracoronary injection of nitroglycerin (Fig. 2). CAG also revealed no significant stenosis in the right coronary artery. Based on the CAG findings, he was diagnosed with coronary spastic angina and benidipine (4 mg, twice daily) was prescribed. After benidipine administration, the patient's symptoms improved and the ECG changes resolved 2 weeks after admission (Fig. 1).

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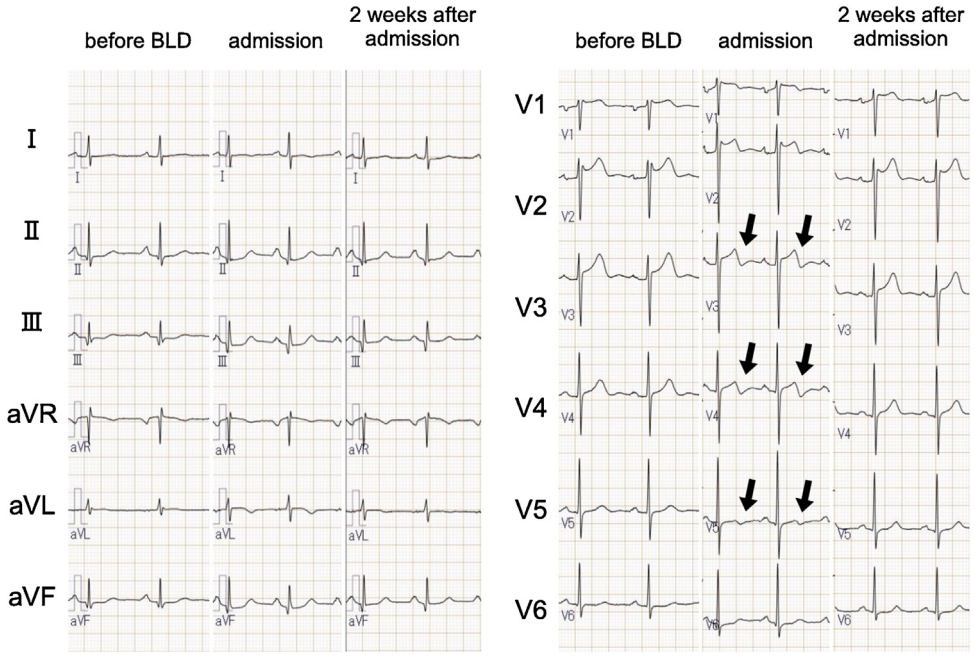

Fig. 1. Twelve-lead electrocardiogram before combination chemotherapy with bortezomib, lenalidomide, and dexamethasone, on admission and 2 weeks after admission. The electrocardiogram demonstrated biphasic T waves in V3–5 on admission (arrow).

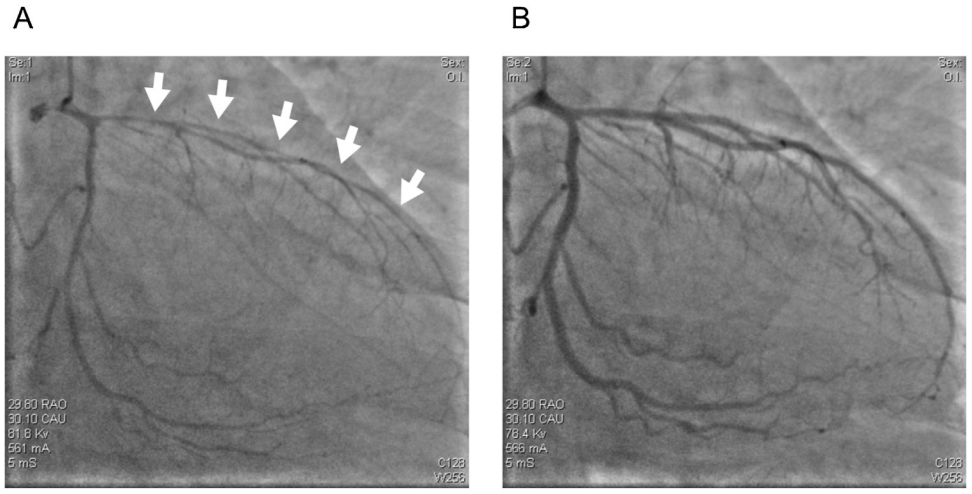

Fig. 2. Left coronary angiogram during emergency cardiac catheterization. (A) Diffuse spasm is observed in the left coronary artery, especially in the left anterior descending artery (arrows). (B) Coronary artery spasm was relieved after intracoronary injection of nitroglycerine.

BLD therapy was restarted in the outpatient setting. Although he experienced mild chest pain once during his sixth BLD therapy cycle, his chest pain resolved with sublingual nitroglycerin administration and did not reoccur. After his seventh BLD therapy cycle, he received high-dose melphalan supported by autologous stem cell transplant and maintenance therapy with lenalidomide.

Discussion

In this report, we present a case of coronary spastic angina that occurred in a patient during BLD therapy for multiple myeloma. Calcium channel blockers (CCBs) prevented further angina attacks, and the patient could continue treatment for multiple myeloma.

This patient was diagnosed with coronary spastic angina according to Japanese Circulation Society guidelines [2]. He presented with effort angina and his ECG findings were borderline. Although drug-induced coronary spasm provocation test was not performed, CAG revealed spontaneous diffuse coronary spasm. We believe that this finding is a clear evidence of myocardial ischemia although the diagnostic criteria for diffuse coronary spasm is not established in Japanese Circulation Society guidelines.

Coronary spastic angina attacks usually appear at rest. Rest angina is caused by total occlusion of a coronary artery. Total vessel

occlusion coinciding with rest angina can be observed in drug-induced coronary spasm provocation test during CAG. Contrarily, this patient presented with exertional chest pain. This could be explained by the observation of diffuse coronary spasm without total occlusion by CAG.

Bortezomib can induce coronary spasm, and the possibility that lenalidomide and dexamethasone contributed to coronary spasm in this patient cannot be overlooked. Proteasome inhibition has been reported to be associated with increased coronary artery oxidative stress [3], and oxidative stress degrades nitric oxide (NO) and causes vasoconstriction [4]. This patient presented with exertional chest pain at a cumulative bortezomib dose of 23.6 mg/m^2. This is in agreement with a previous report that showed that the onset of cardiac symptoms was recorded after a cumulative bortezomib dose of $\geq$20.8 mg/m^2 [5]. Although lenalidomide has not been reported to induce coronary spastic angina, a previous study reported that lenalidomide inhibited VEGF-induced PI3K-Akt signaling [6]. Because endothelial nitric oxide synthase (eNOS) is a downstream target of Akt [7], lenalidomide might inhibit eNOS activation and reduce NO production. Dexamethasone can also induce coronary spastic angina. A previous report described three cases of coronary spastic angina, which occurred soon after the initiation of glucocorticoid therapy [8]. Glucocorticoids sensitize coronary vasoconstriction responses through the activation of Rho-kinase [9]. Therefore, clinicians should be aware of the possible occurrence of coronary spastic angina during BLD therapy for multiple myeloma.

In the present case, CCBs prevented further angina attacks, and the patient could continue BLD therapy for multiple myeloma. Although CCBs are the established treatment for coronary spastic angina [4], to the best of our best knowledge, this is the first report describing the efficacy of CCBs in treating coronary spastic angina in a patient with multiple myeloma during BLD therapy. After completing BLD therapy, the patient received high-dose melphalan supported by autologous stem cell transplant and maintenance therapy with lenalidomide. Thus, the prevention of coronary spastic angina using CCBs may lead to the best possible outcome.

Multiple myeloma can cause cardiac amyloidosis. Angina occasionally occurs in cardiac amyloidosis patients due to amyloid deposition in intramyocardial arteries with luminal obstruction [10]. In such patients, CAG shows no significant stenosis in epicardial coronary arteries, and pharmacotherapy for coronary spastic angina is ineffective. In our patient, CAG revealed diffuse coronary spasm, and CCBs were effective for angina. Based on the findings above, angina was not caused by cardiac amyloidosis in our patient.

In conclusion, BLD therapy for multiple myeloma can induce coronary spastic angina, and clinicians should be aware of this possibility when initiating therapy. CCBs can prevent angina attacks and allow patients to continue treatment for multiple myeloma.

Conflict of interest

The authors declare that there are no conflicts of interest.

Acknowledgement

None.

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