Bevacizumab-Related Microvascular Angina and Its Management with Nicorandil

Manami Katoh,¹ MD, Norihiko Takeda,¹ MD, Takahide Arimoto,¹ MD, Hajime Abe,¹ MD, Katsutoshi Oda,² MD, Yutaka Osuga,² MD, Tomoyuki Fujii,² MD and Issei Komuro,¹ MD

Summary
Bevacizumab, an inhibitor of vascular endothelial growth factor (VEGF)-A, is currently used to treat patients with ovarian or colon cancer. While several cardiovascular toxicities related to bevacizumab-containing regimens have been reported, the effect of bevacizumab on the coronary microcirculation has not been fully elucidated. Here we report a case of a 54-year-old female patient who developed microvascular angina after a series of bevacizumab-containing chemotherapeutic regimen. The discontinuation of bevacizumab and nicorandil administration was effective in alleviating her chest discomfort and the ischemic changes on her ECG. This highlights the possibility that coronary microvascular angina can be induced in patients treated with bevacizumab-containing chemotherapy. It should also be noted that nicorandil can be effective in managing microvascular angina.

Key words: Chemotherapy, VEGF, Avastin

Microvascular angina is defined as the development of angina pectoris due to reduced coronary flow in the very small coronary arteries, while the epicardial coronary arteries remain intact.¹ Impairment of vascular endothelial function or microvascular spasm underlies the onset of microvascular angina.² Bevacizumab, an inhibitor of vascular endothelial growth factor (VEGF)-A, is currently used to treat patients with colon or ovarian cancer.³ While several types of cardiovascular toxicity related to bevacizumab-containing regimens, such as hypertension, thrombus formation, and heart failure, have been previously reported,⁴,⁵ the effect of bevacizumab on the coronary microcirculation has not been clearly elucidated.

Case Report
Here, we report a case of a 54-year-old female patient who developed microvascular angina after bevacizumab treatment. She had no risk factor for ischemic heart disease (IHD) including hypertension, diabetes, dyslipidemia, smoking, and family history for IHD. She was diagnosed with ovarian cancer at our hospital and an adnexectomy was carried out 10 years ago. Following the surgery, chemotherapy with taxane and carboplatin [five courses of paclitaxel (175 mg/m²) ] and carboplatin (AUC 6), and one course of docetaxel (70 mg/m²) and carboplatin (AUC 5) was initiated. Splenectomy was carried out 6 years ago for the treatment of ovarian cancer metastasis, followed by six courses of paclitaxel (175 mg/m²) and carboplatin (AUC 5). We detected the recurrence of her ovarian cancer 2 years ago and administrated nine courses of paclitaxel (175 mg/m²) and carboplatin (AUC 5). After that, because of residual peritoneal dissemination, bevacizumab (1000 mg/body, 15 mg/kg) was given under her excellent performance status. Paclitaxel (175 mg/m²) and carboplatin (AUC 5) were added at initial two courses.

After six courses of bevacizumab-containing chemotherapeutic regimen, we noted that her blood pressure was elevated thereafter, and we started candesartan (4 mg/daily) to control her blood pressure. Moreover, after 21 cycles of bevacizumab-containing chemotherapy, she complained of chest pain which mostly lasted for 1-2 hours at rest. Physical activity did not elicit her chest symptom. She was admitted to another hospital.

Upon admission, her electrocardiogram (ECG) showed negative T waves in leads III, aVF, V3, V4, V5, and V6 (Figure 1A). Her serum troponin level was normal, and her echocardiography showed normal left ventricular systolic function. The plasma level of brain-type natriuretic peptide was 14.0 pg/mL. On coronary angiography (CAG), no significant stenosis was detected in both the left and right coronary arteries (Figure 2A, B). Subsequent intracoronary acetylcholine provocation tested neither induced coronary stenosis nor occlusion. While she felt chest pain during the procedures of CAG, acetyl-
Twelve-lead electrocardiogram revealed negative T waves in leads III, aVF, V3, V4, V5, and V6 (A). After nicorandil treatment, the ischemic ECG changes resolved (B).

Figure 1. Twelve-lead electrocardiogram revealed negative T waves in leads III, aVF, V3, V4, V5, and V6 (A). After nicorandil treatment, the ischemic ECG changes resolved (B).

choline injection did not significantly augment the severity of her symptom. The patient was discharged 5 days later. While bevacizumab-containing chemotherapy was discontinued, she continued to experience chest discomfort thereafter, and as a result was referred to our department. Nitroglycerin spray was used, which partially relieved her chest symptom. Therefore, she was commenced on nicorandil 15 mg per day. After starting nicorandil, her chest discomfort was alleviated significantly, and the ischemic changes on her ECG were resolved (Figure 1B).

Discussion
While no significant stenosis was detected in the epicardial coronary arteries on her CAG, the results of her ECG indicated the presence of myocardial ischemia. The clinical findings of the patient were consistent with the features of microvascular angina. The development of acute coronary syndrome in the epicardial coronary arteries of patients receiving bevacizumab-containing regimens has already been reported, although this is, as far as we know, the first case of the development of microvascular angina in patients treated with bevacizumab. Hypertension is one of the most common side effects of bevacizumab therapy. While endothelial dysfunction seems to be associated with the rise in blood pressure, the precise molecular processes by which bevacizumab induces systemic hypertension still remain uncertain. We and others have known that VEGF-A signaling plays a critically important role in maintaining the integrity of vascular endothelial cells.
Therefore, it could be speculated that a bevacizumab-mediated suppression of endothelial VEGF-A signaling elicited endothelial dysfunction, resulting in the occurrence of hypertension and microvascular angina. Further research is needed to elucidate the molecular link between VEGF-A signaling and the microvascular circulation.

This case highlights the possibility that coronary microvascular angina can be induced by bevacizumab-containing chemotherapy. The fact that nicorandil administration alleviated her clinical symptoms should also be noted. Nicorandil acts not only as a nitrate, but also as an ATP-sensitive potassium channel opener, and is used as an anti-ischemic drug. Nicorandil may also be effective to dilate coronary microcirculation. While calcium channel blockers may not always be effective in treating microvascular angina, nicorandil can be an effective anti-angina drug for the treatment of patients with microvascular angina secondary to the administration of a bevacizumab-containing regimen.

Disclosures

Conflict of interest: None

References