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Acute Myocardial Infarction Induced by Cisplatin-Based Combination Chemotherapy for Malignant Melanoma : A Case Report

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Abstract

A 61-year-old woman with stage Ⅳ malignant melanoma suffered acute myocardial infarction during the third course of chemotherapy with cisplatin, dacarbazine, nimustine hydrochloride and tamoxifen citrate, despite no serious problem occurring during the first and second courses of chemotherapy. Since this patient, excluding menopause, had no significant risk factor for coronary heart disease before the start of chemotherapy, the infarction was likely to be attributable to the chemotherapy regimen. Chemotherapy should be used cautiously in patients with coronary risk factors before treatment is begun.

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Key Words

■**Drug therapy** (**cisplatin**) ■**Neoplasms** (**malignant melanoma**)
■**Myocardial infarction, treatment** (**acute**) ■**Arteries** (**coronary artery calcification**)

INTRODUCTION

Calcific deposits in coronary arteries are pathognomonic of atherosclerosis. Clinical and histopathological studies have confirmed the close correlation between extent of coronary artery calcification and burden of atherosclerotic coronary disease. Epidemiological studies suggest the probability of future cardiac events is closely related to atherosclerotic disease burden. The extent of coronary artery calcification may therefore indicate cardiovascular risk. Cisplatin is one of the most important anticancer agents for solid tumors. Nephrotoxicity of cisplatin may result in increased magnesium excretion, even before renal function becomes affected. We experienced a case of cisplatin-induced acute myocardial infarction at the site of coronary artery calcification in the right coronary

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Table 1 Lipid levels before and after cisplatin-based combination chemotherapy

	Before chemotherapy	Post first course	Post second course	Post third course
Triglyceride (mg/dl)	56	90	144	188
Total cholesterol (mg/dl)	189	213	207	226
High-density lipoprotein-cholesterol (mg/dl)	—	72	69	81
Low-density lipoprotein-cholesterol (mg/dl)	—	134	114	125

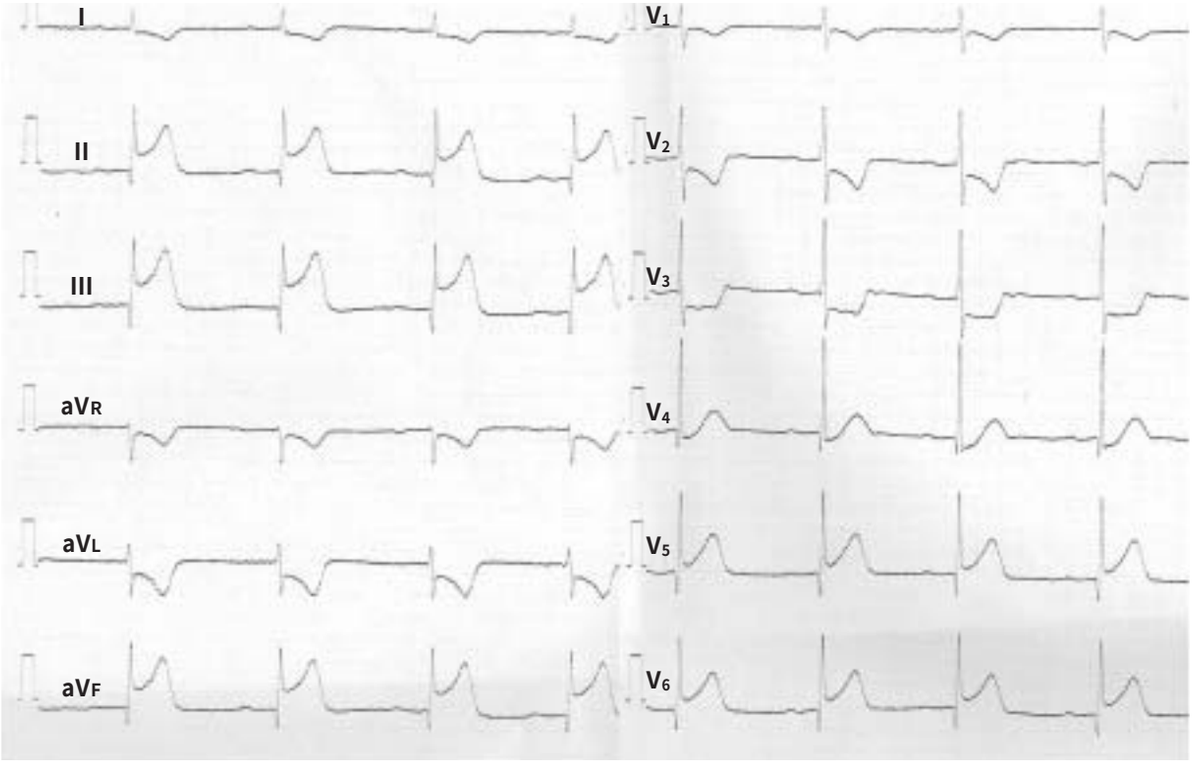

Fig. 1 Electrocardiogram showing marked ST segment elevations in Ⅱ, Ⅲ, aVF, V5 and V6 leads and ST segment depressions in Ⅰ, aVR, aVL and V1−V4 leads

artery.

CASE REPORT

A 61-year-old woman was diagnosed with stage Ⅳ malignant melanoma in June 2003. There was no history of cigarette smoking, diabetes mellitus, or heart, lung or renal disease. This patient, excluding menopause, had no significant risk factor for coronary heart disease. She received the third course of chemotherapy with cisplatin (85 mg/m^2/day, first day), dacarbazine (160 mg/m^2/day, second day to fifth day), nimustine hydrochloride (60 mg/m^2/day, second day) and tamoxifen citrate (20 mg/day, every day). Serum triglyceride values increased during the chemotherapy in our patient (**Table 1**). On day 6 of the third chemotherapy course, she complained of chest pain, and was brought to our department 1 hr after the attack.

Physical examination revealed that her heart rate was 48 beats/min, her systolic blood pressure was 80 mmHg, and lung, heart and abdominal sounds were normal. Electrocardiography showed marked ST segment elevation in Ⅱ, Ⅲ, aVF, V5 and V6 leads and ST segment depression in Ⅰ, aVR, aVL and V1−V4 leads (**Fig. 1**). Left ventricular echocardiography showed inferior to posterior left ventricular wall motion was hypokinetic on the parasternal

long-axis, short-axis and apical long-axis views. Administration of sublingual nitroglycerin, oral aspirin and intravenous isosorbide dinitrate did not reduce her chest pain, or ST segment elevation or depression. We initially suspected acute myocardial infarction based on these clinical data.

Two hr after the onset, cardiac catheterization was performed. The mean pulmonary wedge pressure was 7 mmHg with a cardiac index of 1.48 *l*/min/m^2. Forrester hemodynamic subset was class III. Emergent coronary angiography revealed total occlusion of the proximal portion (segment 1) of the right coronary artery (**Fig. 2**). The intracoronary thrombus were treated with tisokinase (1,600,000 U) by pulse infusion thrombolysis twice. The total occlusion of the culprit lesion improved to Thrombolysis in Myocardial Infarction (TIMI) flow grade 2 (99% delay) after each thrombolysis (**Fig. 3**), but the lesion became total occlusion after a few minutes. Therefore, a RADIUS stent was successfully implanted for segment 1. The peak creatine kinase was 2,147 U/*l* (creatine kinase-MB 245 U/*l*, Trop T Sensitive positive). Anticoagulant and antiplatelet therapy was begun to prevent thrombosis. After the four and fifth courses of chemotheraphy (dacarbazine and nimustine hydrochloride), malignant melanoma went into complete remission.

Follow-up coronary angiography revealed no restenosis at the percutaneous coronary intervention site and left ventriculography showed normal contraction. Subsequently the patient had no recurrence of coronary events or any other thrombotic episodes.

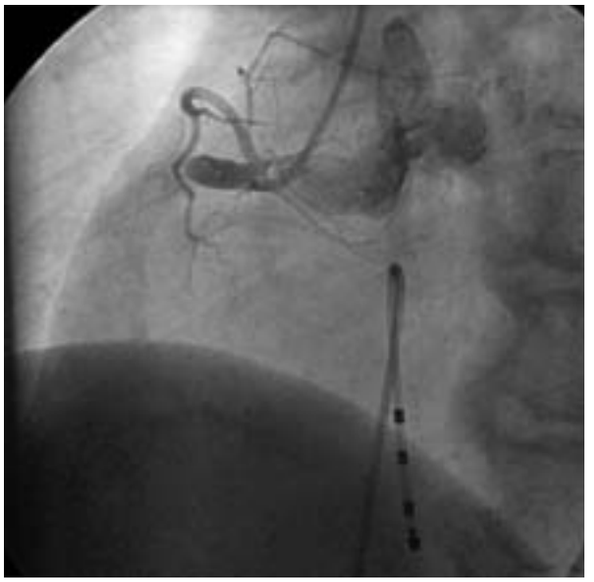

Fig. 2 Coronary angiogram showing total occlusion of the right coronary artery at pre-percutaneous coronary intervention

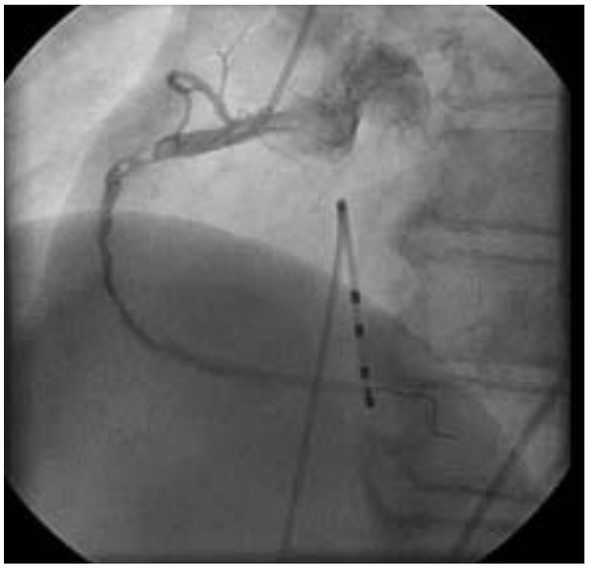

Fig. 3 Coronary angiogram showing intracoronary thrombus after tisokinase (3,200,000 U) administration by pulse infusion thrombolysis
The total occlusion of the culprit lesion improved to Thrombolysis in Myocardial Infarction flow grade 2 (99% delay).

DISCUSSION

Acute myocardial infarction seldom occurs as an adverse drug reaction of a carcinostatic substance. There are several reports of acute myocardial infarction after vincristine, vinblastine, etoposide, cisplatin administration[1–4], and combined therapy of vinblastine, bleomycin, and cisplatin[5]. The present patient showed the symptoms of acute myocardial infarction after cisplatin-based combination chemotherapy for malignant melanoma. Acute myocardial infarction had occurred during the third cisplatin therapy.

Based on endomyocardial biopsy studies, cumulative anthracycline doses are now generally kept lower than 450 mg/m^2, resulting in a risk of clinical symptoms in about 3% of cases. The risk is up to 26% for cumulative doses[6] of 550 mg/m^2. However, there was no reports of risk with cumulative cisplatin dose. In our case, there was no history of cigarette smoking, diabetes mellitus, hypertension, or hyperlipidemia before the start of chemotherapy.

On admission, postmenopause was the only risk factor for coronary heart disease in this patient. Severe intracellular magnesium and potassium depletion have occurred in patients after treatment with cisplatin[7]. Magnesium deficiency is one of the most important triggers of coronary artery spasm in patients with vasospastic angina[8]. Coronary spasm can be a cause of not only variant angina but also ischemic heart disease in general, including unstable angina, acute myocardial infarction and sudden ischemic death[9]. Intracellular magnesium deficiency is also a risk factor of acute coronary syndrome[10]. Regrettably, magnesium level was not measured in this patient. Magnesium level should be measured during chemotherapy with cisplatin.

Serum triglyceride values increased during the chemotherapy in our patient(**Table 1**). Three cases of severe hypertriglyceridemia due to tamoxifen therapy have been reported[11]. The Asia Pacific Cohort Studies Collaboration reported that serum triglyceride level is an important and independent predictor of coronary artery disease and stroke risk in the Asia-Pacific region[12]. These results have clinical implications for cardiovascular risk prediction and use of lipid-lowering therapy.

We recognized that the culprit lesion was thrombus-rich after thrombolysis therapy. Increased thrombotic activity may have been associated with the coronary occlusion in this patient.

Coronary artery calcification is a predictor of increased risk for coronary artery disease[13]. Coronary artery calcification extent on electron beam computed tomography(EBCT)is highly predictive of future hard cardiac events and adds valuable prognostic information in patients undergoing angiography[14]. Coronary artery calcification score can be combined with Framingham score for risk prediction in asymptomatic individuals[15]. Coronary artery calcification measured by EBCT correlates with plaque burden and vessel stenosis, is predictive of future cardiac events in the general population. In our case, multi-detector row helical computed tomography(MDCT)was performed to search for any metastasis. Coronary calcium is intimately associated with coronary atherosclerotic plaque development. Prospective studies have demonstrated that extensive coronary calcium detected by EBCT is associated with a significantly increased incidence of subsequent myocardial infarction, need for revascularization, and coronary death[16]. MDCT revealed a few metastases of malignant melanoma and coronary artery calcification in the right coronary artery(**Fig. 4**). MDCT is comparable to EBCT for coronary calcification screening[17].

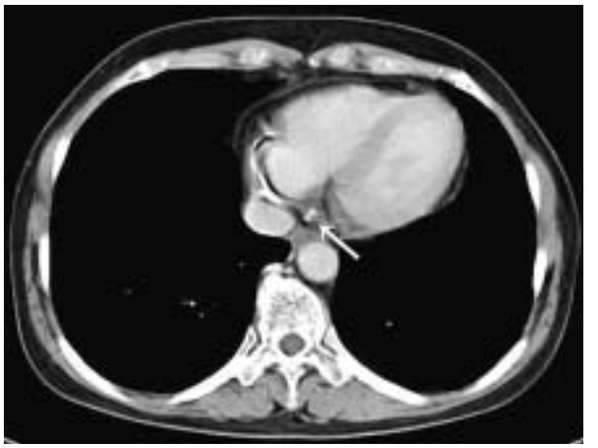

Fig. 4 Transverse multi-detector computed tomography scan showing coronary artery calcification (*arrow*)in the right coronary artery

In conclusion, this patient had three risk factors, postmenopause, hypertriglyceridemia, and coronary artery calcification, for coronary heart disease before the third course of chemotherapy. Chemotherapy should be used cautiously in patients with coronary risk factors before treatment is begun.

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要　　約

悪性黒色腫に対するシスプラチンを主体とした化学療法が関与したと考えられる急性心筋梗塞の1例

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症例は61歳の女性で，悪性黒色腫(Ⅳ期)の診断で第3クール目の化学療法中(シスプラチン，ダカルバジン，塩酸ニムスチン，クエン酸タモキシフェン)に急性心筋梗塞を発症した．当初，閉経後である以外は明らかな冠危険因子が認められなかった．このため今回発症した心筋梗塞は化学療法で使用された薬剤が一つの原因と考えられた．本症例では冠動脈の石灰化の有無や化学療法中の脂質や電解質の動態について，積極的に検討していくべきであったと考えられた．

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