Vasospastic Angina After Chemotherapy by With Carboplatin and Etoposide in a Patient With Lung Cancer

Shuichi Yano, M.D. and Kazue Shimada, M.D.

We report here a case of vasospastic angina following the administration of Carboplatin (CBDCA) and Etoposide (VP-16) in a patient with small cell lung carcinoma. Although these drugs are commonly used to treat small cell lung carcinoma, there has been no previous report of vasospastic angina in a patient without a history of heart disease. Therefore, we should be aware of the possibility that vasospastic angina may develop even in a patient without any history of heart disease. While calcium antagonist and isosorbide dinitrate are generally helpful for preventing vasospastic angina, these drugs could not completely suppress vasospastic angina in this case. (*Jpn Circ J* 1996; **60**: 185–188)

A 69-year-old man was admitted to our medical center in January, 1994, with a three-week history of hemoptysis. A chest roentgenogram showed a right hilar mass shadow. The right intermedius was invaded by the tumor based on bronchofiberscopic findings, and small cell lung carcinoma was histologically diagnosed by transbronchial biopsy. Computed tomography demonstrated mediastinal lymph node metastasis (Fig 1). He had no past history of chest pain, cardiac disease or hypertension. He had smoked for 40 years. A routine electrocardiogram (ECG) revealed normal sinus rhythm with no changes in the ST segment and or T wave (Fig 2A). The fasting plasma glucose level was elevated to 147 mg/dl. Plasma lipid levels were within the normal range. He was initially treated by combined chemotherapy using Carboplatin (CBDCA) (300 mg/m², the 1st day) and Etoposide (VP-16) (100 mg/m², the 1st day to the 3rd day, total 300 mg/m²). He received the same chemotherapy again in February, 1994. About

5 h after the end of anticancer drug infusion on the 1st day of the 2nd chemotherapy, he complained of severe anterior chest oppression, nausea and diaphoresis. ECG showed ST segment elevation in leads I, aVL and V5–6, ST segment depression in V1–4 and T wave inversion in II, III, aVF and V5–6 (Fig 2B). Although arterial blood pressure fell to 80/50 mmHg, symptoms were promptly relieved and the ECG returned to baseline. Two sheets of isosorbide dinitrate tape were attached to prevent further anginal episodes. An echocardiogram showed hypokinesis of the anterolateral left ventricular wall. 2 h after the 1st anginal attack, the same chest symptoms recurred and an ECG showed the same ST segment and T wave changes. A nitroglycerin tablet was given sublingually because arterial blood pressure remained at 114/74 mmHg. However, the symptoms were not completely relieved. Venous infusion of nitroglycerin (0.8 µg/kg per min) was begun by and one bolus of lidocaine (50 mg) was given to treat short-run ventricular tachycardia (Fig 2C). The symptoms were completely relieved after 20 min. Angiography was performed on the

Key words:

Carboplatin
Etoposide
Vasospastic angina

(Received January 10, 1995; accepted June 10, 1995)

The Department of Pulmonary Medicine, Shiga Prefectural Medical Center, Shiga, Japan

Mailing address: Shuichi Yano, M.D., Department of Pulmonary Medicine National Sanatorium Matsue Hospital 5-8-31, Agenogi, Matsue city, Shimane 690, Japan

Fig 1. Chest roentgenogram and computed tomographic scan on admission.

Fig 2. The patient's electrocardiogram during an episode of coronary spasm.

- A. Baseline ECG
- B. Onset of chest pain
- C. Short-run of ventricular tachycardia during anginal attack
- D. Return to normal on the following day

Fig 3. Coronary arteriograms on the day after the ischemic attack.
upper; left coronary arteriogram in right anterior oblique view
lower; right coronary arteriogram in left anterior oblique view

following day. Left ventriculogram revealed normal cardiac function and coronary arteriograms showed no stenosis (Fig 3). The peak serum creatine kinase (CK) levels were slightly increased to 222 IU/L and the peak CK-MB was increased to 28 IU/L (13%). The ECG was normalized by the following day (Fig 2D). The treatment regimen was changed to oral diltiazem (90 mg, tid), isosorbide dinitrate (15 mg, tid) and isosorbide dinitrate tape. After receiving this medication, he had no further anginal episodes during two subsequent courses of chemotherapy. The primary lung mass was markedly decreased and he was discharged from our hospital in April, 1994, after four courses of chemotherapy. He was followed at our outpatient department with oral VP-16 (50 mg daily). In May, 1994, he was hospitalized with sudden-onset severe dyspnea and high grade fever. Radiography of the chest showed interstitial shadow in the all of the lung fields, and he was diagnosed as drug-induced pneumonitis due to oral VP-16. Infusion of methylprednisolone (1000 mg daily for 3 days) resulted in an improvement of the interstitial shadow. Treatment with calcium antagonist and isosorbide dinitrate was maintained. Early in the morning of the 10th day after the 2nd admission, he was found in cardiopulmonary arrest by a nurse, after having complained of chest pain to another patient. Cardiopulmonary resuscitation was initiated without success and he was pronounced dead. An autopsy was not performed.

DISCUSSION

It has been suggested that vasoactive substances induce coronary vasospasm in coronary arteries with injured endothelium¹⁻³. Such a mechanism has been demonstrated in miniature swine and canine models^{4,5} in which the endothelium of the coronary artery was injured by an intracoronary guidewire or balloon. Coronary vasospasm can not be induced by vasoactive substances in a coronary artery with normal endothelium. Recently, we experienced a case of vasospastic angina with no organic coronary artery stenosis confirmed by coronary arteriography after chemotherapy by with Carboplatin (CBDCA) and Etoposide (VP-16).

The symptoms which developed after the 2nd chemotherapy led to a diagnosis of typical angina pectoris based on the changes of in the ECG during the attack. The changes in the ECG during the attack implicated acute anterolateral myocardial ischemia induced by coronary vasospasm. A coronary arteriogram the day after the anginal attack demonstrated intact coronary arteries with no thrombi. Several minutes before cardiopulmonary arrest, he complained of chest pain in the early morning. The episode also suggested vasospastic ischemic attack. Coronary vasospasm secondary to chemotherapy with CBDCA is a rare complication, relative to the cardiotoxicity of other anticancer agents such as doxorubicin, daunorubicin and 5-FU. Myocardial infarction has been reported after infusion of VP-16 in patients with preexisting cardiovascular disease⁶. In addition, there have been reports of myocardial infarction after the administration of Cisplatin (CDDP), an analogue of Carboplatin (CBDCA)⁷⁻⁹. Bodensteiner reported coronary artery occlusions caused by fibrous intimal proliferation 7 months after completing one course of bleomycin, vinblastin and cisplatin therapy⁸. Doll et al described the occurrence of acute myocardial infarction with cisplatin-based chemotherapy in 2 males. Coronary angiography in one of the patients did not demonstrate any endovascular abnormality. However, ergonovine maleate precipitated diffuse coronary spasm and chest pain⁹. Although there has been a previous report of infarction during combined treatment with CBDCA and VP-16, the coronary artery was stenotic due to invasion of the carcinoma¹⁰. There has been no report of angina pectoris being closely related to the administration of CBDCA and VP-16 in patients with no history of heart disease or intact coronary arteries. Although several mechanisms have been suggested with other anticancer agents, the precise mechanism of coronary vasospasm remains unclear. It is well known that the intravenous use of anticancer drugs causes intimal hyperplasia and injures the endothelium of the arterial wall^{8,11,12}. After chemotherapy, injured pulmonary endothelium can not adequately degrade serotonin, and some vasoactive substances, such as serotonin, can induce coronary vasospasm through injured

endothelium. Although it is not clear whether such cardiac events are related to chemotherapy or whether they represent a fortuitous association, we should pay attention to the possibility that vasospastic angina may develop even in patients who do not have any history of heart disease. When middle-aged or elderly patients require anticancer drugs which may injure the endothelium of the arterial wall, premedication with calcium antagonists or isosorbide dinitrate may be helpful in preventing vasospastic angina before anticancer treatment. However, these drugs could not completely suppress vasospastic attack in this case.

REFERENCES

1. Golino P, Piscione F, Willerson JT, Cappelli-Bigazzi M, Focaccio A, Villari et al: Divergent effects of serotonin on coronary-artery dimensions and blood flow in patients with coronary atherosclerosis and control patients. *N Engl J Med* 1991; **324**: 641–648
2. Vanhoute PM: Platelet-derived serotonin, the endothelium, and cardiovascular disease. *J Cardiovasc Pharm* 1991; **17**(Suppl 5): S5–12
3. McFaden EP, Clarke JG, Davies GJ, Kaski JC, Haider AW, Maseri A: Effect of intracoronary serotonin on coronary vessels in patients with stable angina and patients with variant angina. *N Engl J Med* 1991; **324**: 648–651
4. Yamamoto Y, Tomoike H, Egashira K, Nakamura M: Attenuation of endothelium-related relaxation and enhanced responsiveness of vascular smooth muscle to histamine in spastic coronary arterial segments from miniature pigs. *Circ Res* 1987; **61**: 772–778
5. Egashira K, Tomoike H, Hayashi Y, Yamada A, Nakamura M: Mechanism of ergonovine-induced hyperconstriction of a large epicardial coronary artery in conscious dogs a month after arterial injury. *Circ Res* 1992; **71**: 435–442
6. Aisner J, VanEcho DV, Whitacre M, Wiernik PH: A phase I trial of continuous infusion VP16-213 (Etoposide). *Cancer Chemother Pharmacol* 1982; **7**: 157–160
7. Vogelzang NJ, Torkelson JL, Kennedy BJ: Hypomagnesemia, renal dysfunction, and Raynaud's phenomenon in patients treated with cisplatin, vinblastine, and bleomycin. *Cancer* 1985; **56**: 2765–2770
8. Bodensteiner DC: Fetal coronary artery fibrosis after treatment with bleomycin, vinblastine, and cisplatin. *South Med J* 1981; **74**: 898–899
9. Doll DC, Ringenberg QS, Yarbrow JW: Vascular toxicity associated with antineoplastic agents. *J Clin Oncol* 1986; **4**: 1405–1417
10. Hirata H, Mizushima Y, Fujishita T, Tanaka T, Mitsui K, Kobayashi M: Acute myocardial infarction due to subpericardial metastasis and/or chemotherapy of the lung - A case report (in Japanese). *Jpn J Cancer Clin* 1993; **39**(2): 155–159
11. Doll DC, List AE, Greco A, Hainsworth JD, Hande KR, Johnson DH: Acute vascular ischemic events after cisplatin-based combination chemotherapy for germ-cell tumors of the testis. *Ann Intern Med* 1986; **105**: 48–51
12. Ueda E, Sako M, Hirota S: Experimental and clinical study of arterial damage induced by anticancer drug infusion (in Japanese). *Nippon Acta Radiologica* 1992; **52**: 960–970