Vasospastic Angina Likely Related to Cisplatin-containing Chemotherapy and Thoracic Irradiation for Lung Cancer

Masaaki Fukuda*,**, Mikio Oka**, Naomi Itoh*, Toshifumi Sakamoto*, Hideki Mori*, Akira Hayakawa* and Shigeru Kohno**

Vasospastic angina is rarely observed during cancer treatment. The present report describes two males with lung cancer, aged 73 and 61, who developed vasospastic angina during combination treatment of cisplatin-containing chemotherapy and thoracic irradiation. As both patients have smoked and their ages are typical for patients with coronary artery disease, such events may be incidental. However, oncologists should be aware of the possible development of myocardial ischemia during or following administration of antineoplastic agents, especially in elderly patients with pre-existing coronary risk factors or a history of thoracic radiotherapy.

(Key words: antineoplastic agents, 5-HT3 receptor antagonist)

Introduction

Cancer chemotherapy is rarely associated with coronary artery diseases (CAD) compared with the relatively high frequency of hematological and gastrointestinal toxicities, although patients with cancer are usually of similar age to those with CAD. However, few reports have described vascular toxicities including CAD, associated with the use of antineoplastic agents or radiotherapy (1, 2). In these reports, a variety of agents, such as vinca alkaloids, 5-fluorouracil, etoposide and cisplatin, were used either singularly or in combination (3). In the present report, we describe two cases of vasospastic angina probably related to cisplatin-containing chemotherapy with thoracic irradiation for lung cancer.

Case Report

Patient 1

A 73-year-old male was admitted to our hospital in July 1996, for further evaluation of an abnormal shadow detected on routine chest radiograph. The patient, who was a smoker (20 cigarettes a day for 53 years), developed a cough with bloody sputum in May 1996. A chest radiograph showed a mass in the left upper lung field apicomedially. The tumor was cytologically diagnosed as adenocarcinoma, and the clinical stage was evaluated as IIIA (cT3N0M0). Thoracotomy was performed on August 20, 1996. The tumor, 6.5 x 5.5 x 3.0 cm in size, was located in the left apicoposterior segment. The left upper lobe was partially resected, since the tumor and the enlarged mediastinal lymph nodes were densely adherent to the mediastinum and the parietal pleura. The surgical stage was finally evaluated as IIIB (sT4N2M0). Postoperatively, combination chemotherapy with cisplatin (80 mg/m² i.v. on day 1) and vindesine (3 mg/m² i.v. on day 1) was begun on September 18, together with thoracic irradiation (2 Gy per day) which commenced on day 3 (Fig 1A). On day 1 the patient received 3.5 liters of intravenous fluids and diuretics for over 12 hours. On days 2, 3, 4, and 5 he was given 2 liter of fluids for 8 hours. Granisetron (3 mg) was also administered intravenously before and after chemotherapy on day 1, and 4 mg of ondansetron was administered orally everyday between days 2 and 7. However, the patient developed severe emesis on day 3 and had acute-onset syncope with diaphoresis and chest oppressive feeling in the early morning of day 4. The electrocardiogram (ECG) showed ST segment elevation in leads II, III, V_5, V_6, and V_1 with ventricular arrhythmia (Fig. 2A), which had not been observed in the prechemotherapy ECGs. Cardiac enzymes were all within normal limits, and systolic arterial blood pressure had fallen to 76 mmHg. However, the symptoms and ECG findings gradually resolved within 48 hours following the administration of a calcium antagonist, nitroglycerin tape and lidocaine (Fig. 2B). At that time, angina pectoris of variant form was diagnosed. Chemotherapy and irradiation were discontinued, though he had no further anginal episodes.
Vasospastic Angina Related to Chemoradiation

### Patient 1

A 61-year-old male smoker (25 cigarettes/day for 35 years) was admitted to our hospital in October 1995 with arm and facial swelling, dyspnea and hoarseness. During the clinical examination at a local hospital, a large mass shadow was detected on a chest radiograph. Physical examination on admission showed edema of the face and neck, engorged veins in the neck and chest, and diminished respiratory sounds in the right lung field. A chest radiograph showed a large mass in the right hilum associated with elevation of the ipsilateral diaphragm. The tumor was histologically diagnosed as small-cell carcinoma by transbronchial biopsy, and the clinical stage was evaluated as a limited disease (T4N3M0). Combination chemotherapy with cisplatin (80 mg/m² i.v. on day 1) and etoposide (100 mg/m² i.v. on day 1–3) together with radiotherapy of the chest commenced on October 23, 1995 (Fig. 1B). Hydration was also given as in Patient 1. Granisetron and ondansetron were administered in a manner similar to the schedule used in Patient 1 above. Radiotherapy (42 Gy in 21 daily fractions, 5 fractions per week) was administered to the tumor-bearing area including the mediastinum, and the tumor markedly regressed following two courses of chemotherapy. On day 7 of the third course the patient developed syncopal attack, diaphoresis and severe chest oppressive feeling. The pulse rate decreased to 48 beats/min, and the systolic blood pressure fell to 56 mmHg. ECG taken immediately after the chest oppressive feeling showed ST segment elevation in leads II, III, V₅, V₆, and V₇, with ventricular arrhythmia. (B) ECG taken 4 days after the above episode. later, the fourth course of chemotherapy was administered but no ischemic event was noted.

### Discussion

In cancer patients, CAD is usually due to atherosclerotic changes affecting arterial walls rather than due to non-atherosclerotic mechanisms, since cancer is usually more prevalent in elderly than young patients. Thus, the underlying mechanisms of CAD in cancer patients who are treated with anticancer agents may include [1] coexistent coronary atherosclerosis, [2] coronary compression or embolization by the tumor, [3] tumor-associated hypercoagulopathy, [4] vasculitis, [5] non-bacterial thrombotic endocarditis, and [6] complications directly related to antineoplastic therapy (4, 5). In the present two cases, vasospastic angina was probably caused by a pre-existing atherosclerotic CAD, radiation-induced CAD, or a direct effect of cisplatin, etoposide or vindesine on the heart. In addition, the vasospasm may be due to the administration of serotonin-antagonist antiemetics used during management of these patients such as oral ondansetron or intravenous granisetron as reported previously (6, 7). However, the vasospastic angina is likely to be caused by cisplatin-containing chemotherapy and/or thoracic irradiation, although the exact mechanism was not determined precisely in the present study. In patient 1, as the recovery of symptoms and ECG changes were delayed, myocardial damages were also considered. However, the patient was diagnosed with vasospastic angina because of the normal
Fukuda et al

Figure 3. (A) Electrocardiogram (ECG) taken immediately after chest oppressive feeling in Patient 2. Note ST segment elevation in leads II, III, and aVF, and V₄, ST depression in leads I and aVL, and complete AV block. (B) ECG taken 5 hours after the above episode.

The two cases described in this report indicate that clinicians should be aware of the potential, although uncommon, development of CAD in cancer patients who are treated with antineoplastic agents. Further documentation of such CAD cases will be necessary to elucidate the mechanisms of this toxicity.

References