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Electrocardiographic Changes Simulating Acute Myocardial Infarction or Ischemia Associated with Combination Chemotherapy with Etoposide, Cisplatin, and 5-Fluorouracil

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Three cases of cardiotoxicity manifested by chest pain, tachycardia, respiratory distress, and electrocardiographic changes simulating acute myocardial infarction or ischemia were observed during the course of combination chemotherapy with etoposide, cisplatin, and continuous infusion of 5-fluorouracil in patients with advanced non-small cell lung cancer. There was no cardiac enzyme elevation. A similar but rare clinical syndrome has been described in association with 5-fluorouracil infusion as a single agent or in combination with other chemotherapeutic agents. We describe the cases and review their possible pathogeneses and clinical implications.

Key Words: *Cardiotoxicity, 5-Fluorouracil, Cisplatin, Etoposide*

INTRODUCTION

A syndrome of angina with variable electrocardiographic (EKG) changes has been described after chemotherapy with 5-fluorouracil (5-FU), either alone or in combination[1~9]. Labianca et al. reported 17 such cases among 1083 patients (1.8%), and Pottage et al. reported 4 cases among 140 patients (2.8%), suggesting that this syndrome occurs infrequently. Recently, a similar syndrome with EKG changes simulating acute myocardial infarction or ischemia was observed in 3 patients treated with a regimen consisting of continuous infusion 5-FU, etoposide, and cisplatin. Given the general trend of the increased use of 5-FU infusion therapy, particularly in combination with cisplatin, this unusually high incidence of 5-FU associated cardiotoxicity needs wide recognition among clinical oncologists and cardiologists.

CASE REPORT

1. Patient 1

A 65-year-old previously healthy woman with no known history of arteriosclerotic heart disease was diagnosed in February 1985 as having undifferentiated carcinoma in the left lower lobe of the lung with multiple bone metastases. There was a weight loss of 20 lb over a 6-month period.

Outpatient chemotherapy was given with cisplatin 70 mg/m^2 intravenously on the first day, and etoposide 60 mg/m^2 intravenously daily for 5 days, along with 5-FU 800 mg/m^2 continuous intravenous infusion daily for 5 days. On the fifth day of chemotherpay, she was admitted with intractable nausea, vomiting, dehydration, and an EKG showing an ST elevation in the precordial leads (Fig. 1A). There was no chest pain on admission. Blood pressure was 130/70, pulse rate 105/min, respiratory rate 20/min, and temperature 36.5°C. The heart had regular rhythm without murmur or gallop. There were fine rales in both lung bases. Laboratory studies showed sodium 132 mEq/L, potassium 2.4 mEq/L, chloride 79 mEq/L, bicarbonate 32 mEq/L, the urea nitrogen 65 mEq/L, and serum creatinine 2.2 mg/dl. The magnesium level was not obtained. The patient was treated with antiemetics and intravenous fluid with clinical improvement and correction of electrolyte abnormalities.

On the third hospital day, the patient complained of precordial pain. The EKG showed a persistent ST-elevation in the percordial leads (Fig.

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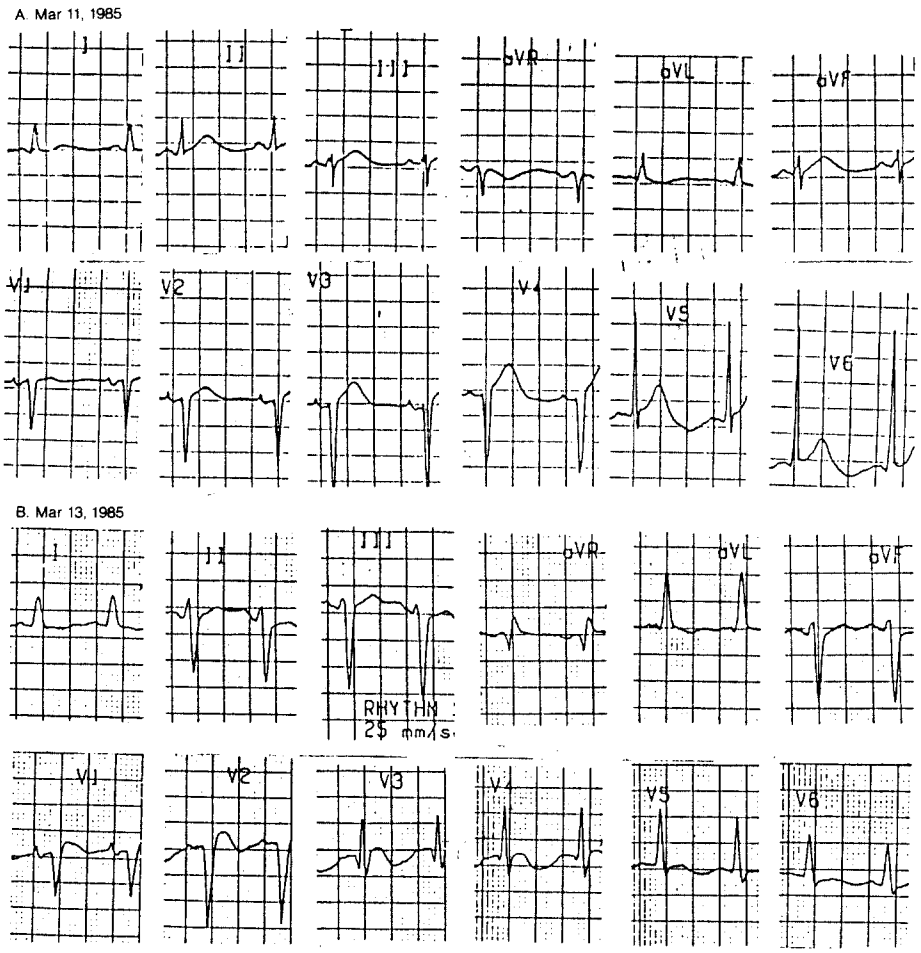

Fig. 1. *Initial EKG (A) shows ST segment elevation in the precordial leads and further change 2 days later (B).*

1B). Serial cardiac enzyme stayed within normal limits. Despite supportive care, the patient expired the next day.

2. Patient 2

A 62-year-old woman, a 40-pack-year smoker with no known history of arteriosclerotic heart disease, was found to have adenocarcinoma of the right middle lobe of the lung with a metastatic disease of the left femur in January 1985. At that time the patient had an unremarkable EKG (Fig. 2A).

Chemotherapy was started on February 13, 1985 according to the same dose and schedule as the previous case. On the fourth day of the fourth course of chemotherapy, the patient suddenly experienced the onset of chest pains and shortness of breath associated with nausea and vomiting. Blood pressure was 100/60, pulse rate 120/min, and respiratory rate 40/min. Cardiac examination was not remarkable except for tachycardia. The EKG showed an ST segment elevation in the precordial leads (Fig. 2B). The serum sodium was 126 mEq/L, potassium 4.8 mEq/L, chloride 90 mEq/L, bicarbonate 30 mEq/L, and the magnesium 0.8 mEq/L. The 5-FU infusion was discontinued, and the patient was treated with diuretics and morphine with clinical improvement. Magnesium was supplemented gradually to 1.9 mEq/L 4 days later. Cardiac enzymes stayed within the normal limits. The EKG remained abnormal with an ST-elevation and T-wave inversion for 3 months, at

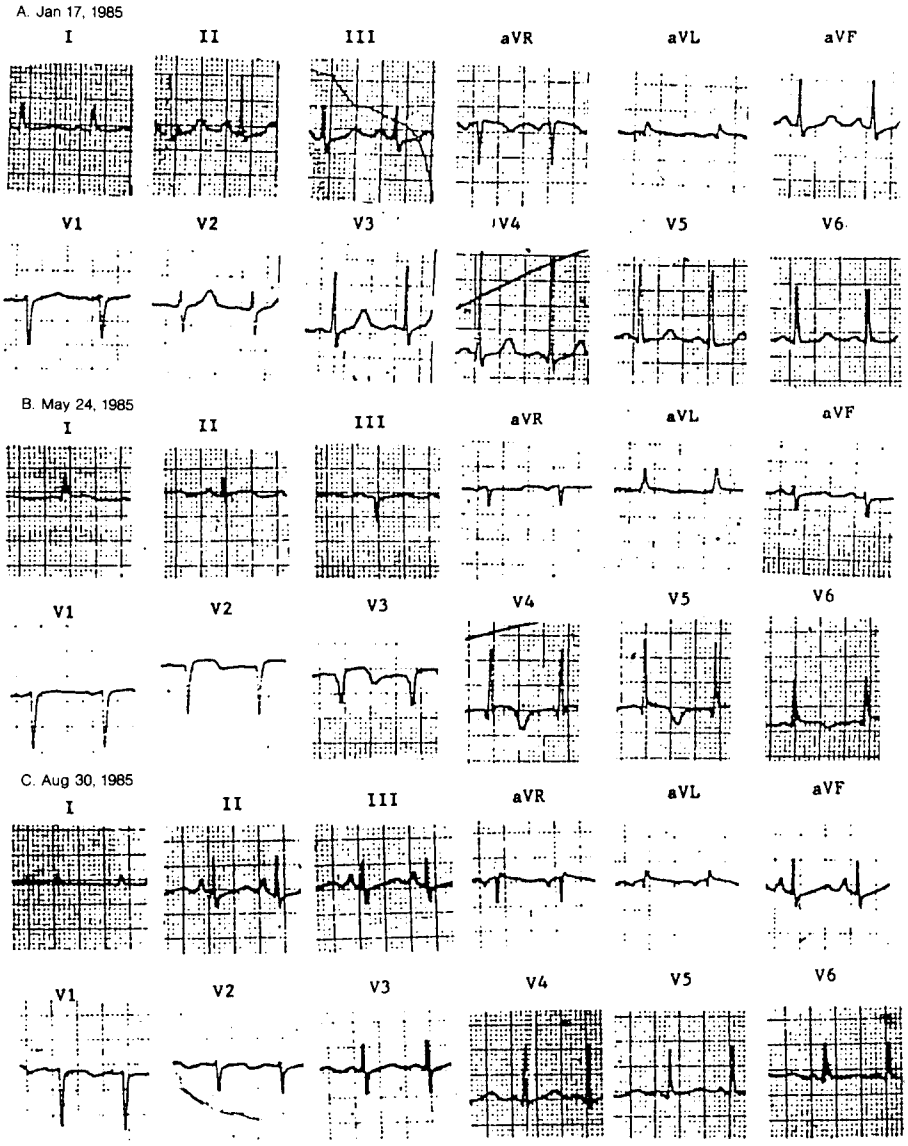

Fig. 2. *Prechemotherapy EKG (A) and EKG at the time of chest pain (B) which shows ST segment elevation and T wave inversion precordially, and EKG 3 months later (C) which shows persistent ST-T changes.*

which time the EKG showed only non-specific changes of ST-T segment (Fig. 2C).

3. Patient 3

A 36-year-old man with no known history of coronary heart disease was diagnosed in September 1984 as having poorly differentiated adenocarcinoma of the right middle lobe of the lung with right hilar and paratracheal lymph node involvement. Pre-treatment EKG was normal (Fig. 3A). The patient received radiation treatment to the mediastinum and right hilar area (5000 rad).

About 2 months after completion of radiotherapy, he was found to have metastatic disease of the right scapula and liver. Chemotherapy was started on February 12, 1985 according to the previously described dose and schedule. On the fifth day of chemotherapy the patient became hypotensive and

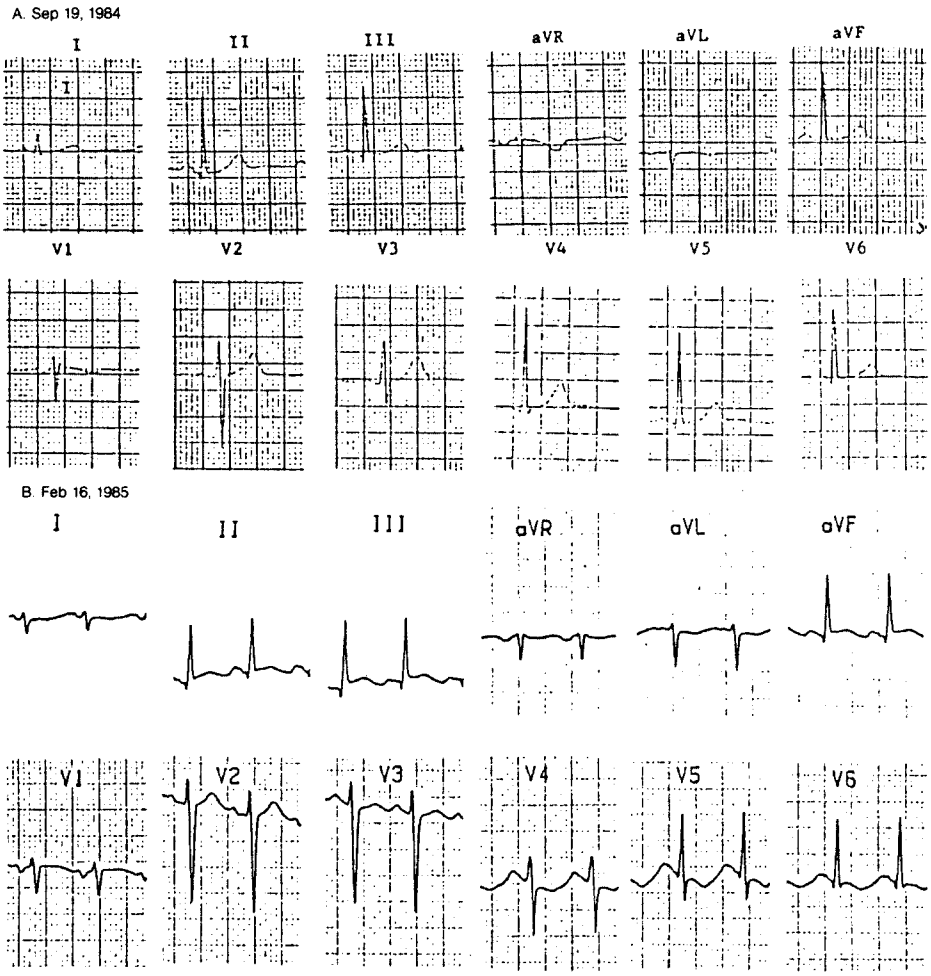

Fig. 3. *Prechemotherapy EKG (A) and EKG during chemotherapy (B) which shows ST elevation in leads* II *and* III *and ST depression in the precordial leads.*

developed apneic episodes. There was no chest pain. Sysptolic blood pressure was 85 mmHg, pulse rate 120/min, are respiratory rate 22/min. The serum sodium was 139 mEq/L, the potassium 3.4 mEq/L, the chloride 99 mEq/L, the carbon dioxide 25 mEq/L, the blood urea nitrogen 35 mg/dl, and the serum creatinine 2.3 mg/dl. The EKG showed sinus tachycardia with ST segment depression in the lateral precordial leads (Fig. 3B). Chemotherapy was discontinued. The patient was stabilized with intravenous fluid and supportive measures including oxygen.

DISCUSSION

Cardiotoxicity of anthracycline antibiotics has been well described and characterized by dose related chronic cardiomyopathy with pump failure or acute toxicities manifested by arrhythmias ranging from supraventricular tachycardia to ventricular tachycardia and various conduction defects. ST segment and T wave changes are also described. Chest pain is not a common manifestation[10~12]. High dose cyclophosphamide caused acute myocardial necrosis with a drop in the EKG voltage and progressive pump failure[13].

There have been reports of chest pain with variable EKG changes in association with 5-FU infusion[1~9]. In a series of Pottage et al. the incidence was 2.8% (4/140 patients). The patients were given bolus intravenous 5-FU infusion as a single agent and developed chest pain 3 to 18 hours after

exposure. There were recurrent episodes of chest pain upon reexposure in 3 patients. EKG changes consisted of ST elevation or T wave changes[5]. Baker et al. reported a case of a 5-FU associated chest pain with EKG change where hemodynamic studies showed evidence of a left ventricular dysfunction with systemic hypotension and elevated mean pulmonary wedge pressure. On autopsy there was no myocardial necrosis or significant arteriosclerotic coronary disease[9].

Because of the rarity of these cases and the lack of apparent dose-response relationship, the cardiotoxicity of 5-FU is not well-established. There is no documented 5-FU induced morphologic changes on histologic examination. Although the underlying mechanism of 5-FU induced EKG changes and chest pain is not clear, it was thought that 5-FU might have a direct toxic effect on the myocardium or cause an autoimmune response against the pericardium or myocardium[4]. Coronary artery spasm is also strongly suspected with reproducible chest pain by repeated exposure to 5-FU[1,5,7].

In our cases, there were several clinical characteristics different from the usual spasm-induced angina. In Patient 1, the EKG changes occurred 2 days before the onset of chest pain, and in Patient 2, the EKG changes persisted several months after the episode of chest pain, although there was no evidence of myocardial infarction by serial cardiac enzyme measurements. In an animal study, 5-FU has been shown to induce electrocardiographic changes suggestive of ischemia in guinea pigs after a latent period of around 3 hours after intravenous infusion. There was higher incidence of electrocardiographic changes with a higher dose of 5-FU[14]. In that study, Matsubara et al. demonstrated that high-energy phosphate compounds were depleted in 5-FU treated myocarium in a dose-dependent fashion, and it was postulated that 5-FU caused metabolic derangement in the myocardium by direct toxicity. The EKG changes were felt to be secondary to the abnormal electrical activity in the cell membrane rather than due to the myocardial ischemia.

In view of the low incidence of reported cases of 5-FU associated angina, occurrence of 3 cases in a short time period in a single institution seems unusual. There might be a synergistic toxic effect between the 5-FU and cisplatin or the 5-FU and etoposide. There are few case reports suggesting endovascular toxicity of cisplatin[15,16]. Also, cisplatin-induced electrolyte imbalance and magnesium depletion might be a predisposing factor for the observed EKG changes. The use of compination chemotherapy with cisplatin and 5-FU with or without etoposide increases in patients with head and neck cancer and other solid tumors because of their synergistic antitumor activities. Potential cardiotoxicity of this combination chemotherapy regmen requires wide recognition among clinical oncologists and cardiologists. Further investigation of the underlying mechanism is also warranted.

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