Coronary Artery Spasm after Intraperitoneal Administration of Cisplatin and Etoposide during Anesthesia

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(Key words: coronary artery spasm, antineoplasmic agents, general anesthesia)

Coronary artery spasm plays an important role in the genesis of myocardial ischemia. While the precise mechanism has not yet been fully elucidated, during perioperative period several causes of coronary artery spasm have been reported, including hyperventilation, injection of calcium salts, low temperature, direct mechanical irritation, and activation of vasovagal reflexes[1–3].

Vascular complications associated with antineoplasmic agents are being reported with increasing frequency, such as myocardial infarction[4–6], thrombotic microangiopathic syndrome[7], and Raynaud's phenomenon[8].

We report a case in which coronary artery spasm, probably related with intraperitoneal administration of cisplatin and etoposide, occurred in a patient under general anesthesia for resection of ovarian tumor without previous history of coronary disease.

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Case Report

A 54-yr-old woman, 157 cm and 54 kg, was admitted for resection of ovarian tumor. The patient had four previous operations for ovarian tumor without any problems. And she was treated 1 month interval with two cycles of cisplatin 20 mg on days 1 through 5 intravenously over a 60-minute period. She has never experienced chest pain and had no significant risk factors for atherosclerotic cardiovascular disease. Her blood pressure was 126/76 mmHg, and heart rate was 74 beats per minute (bpm). Chest roentgenogram and electrocardiogram showed no abnormality. The hemoglobin level was 12.6 $g \cdot dl^{-1}$, with serum albumin 4.2 $g \cdot dl^{-1}$. Serum potassium and magnesium levels were 3.5 $mEq \cdot l^{-1}$ and 1.4 $mg \cdot dl^{-1}$ (normal range: 2.0–2.8 $mg \cdot dl^{-1}$), respectively.

The patient was premedicated oral diazepam 10 mg and ranitidine 150 mg 2 hr before induction of anesthesia. Epidural tubing was performed at the T11-12 intervertebral space, and 10 ml of 1.5% lidocaine with 1:200,000 epinephrine was given. Anesthesia was induced with thiopental 250 mg IV, and vecuronium 6 mg IV was used to facilitate endotracheal intubation. In-

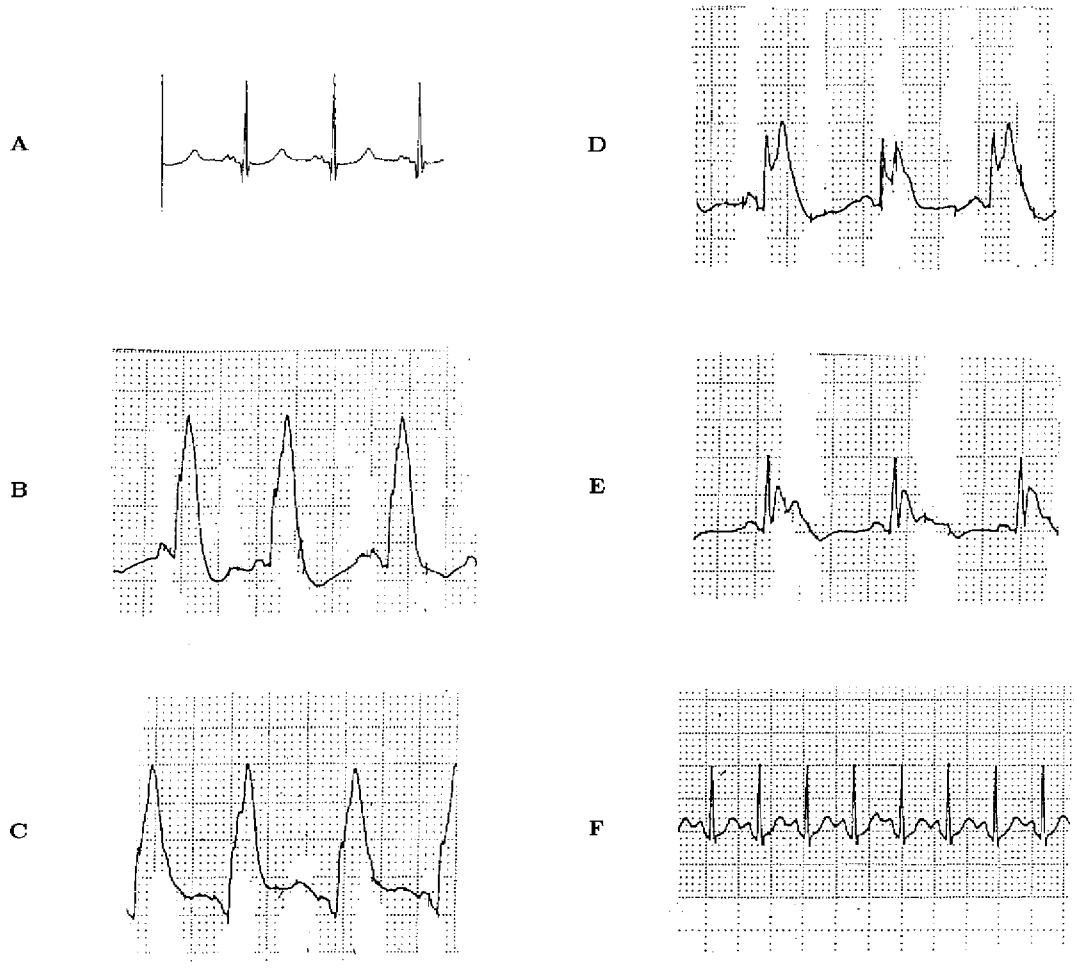

Fig. Electrocardiographic changes during the episode.
A: before induction of anesthesia (lead CM5). B: a few minutes after the intraperitoneal administration of cisplatin and etoposide, showing a marked ST-elevation. C: 4 min after the cardiac massage. D: 6 min after the cardiac massage. E: after injection of diltiazem 2.5 mg and nitroglycerine 100 μg. F: 20 min after the cardiac massage, showing normal ST-segment.

termittent positive pressure ventilation was instituted. Anesthesia was maintained with nitrous oxide (60%) with oxygen and sevoflurane (1.0%), and vecuronium bromide was given for muscle relaxation when indicated. Continuous intraoperative monitoring included electrocardiogram (ECG) with modified V5 lead (CM5), Sp_{O_2} by a pulse oximeter, ET_{CO_2} by a capnometer, direct blood pressure at the radial artery, central venous pressure from right internal jugular vein, and nasopharyngeal temperature.

After induction of anesthesia, the patient was hemodynamically stable and had no evidence of impaired gas exchanges. Two hrs after operation was started, arterial blood gas analysis revealed pH, 7.48; Pa_{CO_2}, 31 mmHg; Pa_{O_2}, 260 mmHg; Base excess, 0.4 mEq$\cdot l^{-1}$. Serum potassium and calcium were 3.1 mEq$\cdot l^{-1}$ and 1.12 mEq$\cdot l^{-1}$, respectively. Lactated Ringer's solution 2,500 ml were infused, and the estimated blood loss was 150 ml.

A few minutes after the intraperitoneal administration of cisplatin 50 mg and etoposide 100 mg, her systolic blood pressure decreased rapidly from 90 mmHg to 50 mmHg. ECG showed marked ST elevation by 0.6 mV with sinus rhythm (fig.). Heart rate decreased from 70 to 55 bpm. The lungs were fully ventilated with 100% oxygen. Ephedrine 15 mg IV elicited no response. While dopamine and dobutamine 8 $\mu g \cdot kg^{-1} \cdot min^{-1}$ each were initiated, arterial blood pressure remained 45/15 mmHg, and heart rate 48 bpm. Norepinephrine 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ was started and external cardiac massage was performed.

Restoration of blood pressure to 135/64 mmHg was achieved within 4 min. ST elevation (0.4 mV) was still remained, and heart rate increased to 120 bpm. Since the occurrence of coronary artery spasm was strongly suspected from its characteristic onset and the ECG change, bolus injections of both diltiazem 2.5 mg and nitroglycerine 100 μg was given and ST-segment returned to the baseline. Continuous administration of nitroglycerine 0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 3 hr was followed. During cardiac massage, blood gas analysis showed pH 7.33; Pa_{CO_2}, 47 mmHg; Pa_{O_2}, 291 mmHg; Base excess, -0.3 $mEq \cdot l^{-1}$; Hemoglobin was 11.8 $g \cdot dl^{-1}$, and serum potassium was 3.1 $mEq \cdot l^{-1}$. There was no evidence of skin flush, or increased airway resistance.

The surgery was completed in 10 min after the episode. Chest roentgenogram showed no abnormal sign. The patient was transferred to the intensive care unit, and was carefully observed for 24 hr. Four hrs after her admission to the intensive care unit, endotracheal tube was extubated after reversal of muscle relaxation by atropine 0.5 mg and edrophonium 30 mg. The patient was fully conscious and was responded well to our verbal commands. Arterial blood gas analysis was within normal limits, and the ECG showed no sign of myocardial ischemia.

Results of serum enzyme studies (SGOT, LDH, CPK) obtained 30 min after admission to the intensive care unit were normal, indicating absence of myocardial infarction. Continuous Holter ECG monitoring was performed for 2 days and her ECG remained within normal limits. The patient was discharged on the 24th postoperative day without any neurological abnormality.

Discussion

In this case, coronary artery spasm was strongly suspected because of a sudden ischemic change in ECG with concomitant circulatory collapse, which was improved immediately by TNG and diltiazem administrations. During perioperative period several causes of coronary artery spasm have been reported, including hyperventilation[9], hypomagnesemia, alpha-adrenergic reaction[10], injection of calcium salts, low temperature, direct mechanical irritation, and activation of vasovagal reflexes[1-3].

The primary cause of the coronary artery spasm that developed in our patient is not clear. However the timing of the coronary spasm that corresponded to intraperitoneal administration of cisplatin and etoposide suggests that this episode may be due to the ischemic vascular complication of antineoplasmic agents[11].

In the past few years, it has become increasingly apparent that the administration of antineoplasmic agents are associated with cardiovascular complications. Among these complications, acute arterial ischemic events were reported after cisplatin-based combination chemotherapy. Doll et al.[12] described the occurrence of acute myocardial infarction associated with cisplatin-based chemotherapy in two young males, aged 25 and 27, neither

of whom had significant risk factors for atherosclerotic cardiovascular disease. Coronary angiography performed in one of his patients did not demonstrate any endovascular abnormality. However, ergonovine maleate precipitated diffuse coronary spasm and chest pain. Bodensteiner[13] reported a patient who had fatal coronary artery disease 7 months after completing one course of cisplatin-based therapy. Coronary angiography had been normal 8 months before the infarction and coronary artery occlusions by fibrous intimal proliferation were demonstrated by necropsy. Vogelzang et al.[14] reported a 24-year-old testicular cancer patient who suffered a fatal myocardial infarction 12 months after completing six cycles of cisplatin-based treatment. Tsutsumi et al.[15] also reported 3 cases of acute myocardial infarction induced by cisplatin and etoposide.

In this case, she had no previous history of coronary disease, nor had significant risk factors for atherosclerotic cardiovascular disease. However, she was treated twice by intravenous cisplatin before surgery, which might have had a potential hazard to the atherosclerotic change to coronary vessels and endothelial cell injury to cause coronary artery spasm as Doll et al.[16] suggested in spite of no history of ischemic episode.

However, the exact mechanism of coronary spasm induced by cisplatin and etoposide in this case is still unclear. It is known that magnesium appears to play an important role in the maintenance of vascular smooth muscle tone. Therefore, hypomagnesemia may potentiate arterial spasm[16], and is a frequent accompaniment of cisplatin therapy. In man hypomagnesemia is associated with sudden ischemic heart death[17]. In dogs magnesium deficiency has been implicated in the triggering of coronary artery spasm[18]. In the laboratory study, the absence of magnesium in the medium significantly potentiated the contractile responses of both small and large coronary arteries to norepinephrine, acetylcholine, serotonin, angiotensin, and potassium[19]. It was therefore suggested that in our patient hypomagnesemia (1.4 $mg \cdot dl^{-1}$) already present preoperatively could have worsened coronary vasospasm caused after the intraperitoneal administration of cisplatin and etoposide.

Since large coronary arteries are abundantly supplied with alpha-receptors, stimulation of alpha-adrenergic receptors results in coronary vasoconstriction[20]. And heightened alpha-adrenergic tone from autonomic dysfunction has been reported after treatment with cisplatin[21], which may also be involved in the mechanism to cause coronary artery spasm in this case.

Hyperventilation causes coronary vasoconstriction in both normal subjects and patients with stable angina pectoris[22]. An excessive decrease of Pa_{CO_2} with concomitant decrease in hydrogen ion concentration is a potential cause of coronary vasoconstriction, since for the same active sites at the transmembrane calcium transport system hydrogen ion competes with calcium ion which activates myofibrillar ATPase of vascular smooth muscle to contract[23]. In this case, before the episode her arterial blood gas analysis showed slight hyperventilation with Pa_{CO_2} 31 mmHg, and pH 7.33. This may be anothr contributing factor to the coronary spasm in this patient.

In summary, we reported a case of coronary vasospasm most likely caused by the intraperitoneal administration of cisplatin and etoposide under general anesthesia. Hypomagnesemia and hyperventilation may also be involved in the mechanism of this episode.

(Received Nov. 19, 1992, accepted for publication Feb. 16, 1993)

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