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SHORT COMMUNICATION

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Carboplatin hypersensitivity presenting as coronary vasospasm – a case report

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Abstract A 68-year-old female patient with advanced ovarian carcinoma collapsed whilst receiving a carboplatin and cyclophosphamide infusion. This reaction was considered to fit with coronary vasospasm. Hypersensitivity to carboplatin is a rare but real complication of therapy and should be considered in patients presenting with hyperacute changes on ECG whilst receiving carboplatin therapy.

Keywords Carboplatin · Hypersensitivity

Introduction

Most of the available antitumor agents can produce hypersensitivity reactions, and several drugs can cause hypersensitivity reactions that are sufficiently frequent to be a major treatment-limiting toxicity. Many other antitumor drugs produce such reactions only sporadically. Whilst L-asparaginase and members of the taxane group of drugs are the usual culprits for hypersensitivity reactions, a number of other chemotherapeutic agents are known to produce hypersensitivity reactions at least sporadically. Most of these reactions have the features of a type I hypersensitivity, whether mediated by IgE or nonimmunologically.

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We report here a case of hypersensitivity presenting as coronary vasospasm during a carboplatin infusion.

Case report

A 68-year-old female patient with advanced ovarian carcinoma collapsed whilst receiving an infusion of 450 mg carboplatin mixed in 1 l 5% dextrose in water. Ondansetron 8 mg, methylprednisolone 500 mg, ranitidine 50 mg, and cyclophosphamide 1.2 g had been administered prior to the carboplatin infusion. She had no previous history of cardiac episodes, nor any cardiac risk factors, and was a nonsmoker. An early breast cancer had been diagnosed and mastectomy performed 15 years prior to the diagnosis of ovarian cancer. At the time of initial diagnosis of ovarian cancer 3 years previously, nonresectable tumor had been noted throughout the abdominal cavity. Initially her CA-125 had been greater than 2000 IU/l with a small increase in CA-15-3. She had been treated at that time with paclitaxel and carboplatin with no obvious changes in her hemodynamics. However, she later admitted to feeling light-headed on a few occasions during the infusion of chemotherapy.

Initially the patient was unconscious with no pulse palpable. She was cold and clammy with an S3 and S4 heard. The initial ECG showed hyperacute ST elevation with reciprocal ST depression anterolaterally, a picture compatible with acute myocardial infarction. Atropine 1 mg and adrenaline 1 mg were injected intravenously.

The patient was transferred to the ICU. Clinically the patient was in shock with a blood pressure of 85/45 mmHg and a pulse rate of 103/min. She also had a massive right pleural effusion. There had been no other signs or symptoms relating to a hypersensitivity reaction (bronchospasm or rash). She was given 300 mg aspirin orally and Ringer's lactate boluses. Her blood pressure responded favorably. Prior to initiation of fibrinolysis, an ECG was performed which showed complete resolution of her ST elevation. The patient was treated with subcutaneous enoxaparin 1 mg/kg twice daily. ECG and cardiac enzymes were repeated 6-hourly and they remained normal. A cardiac echo showed a normal ejection fraction with a sclerotic, calcified aortic valve with a 0.8-cm nodule on the valve and mild aortic incompetence. The picture quality was not optimal as the patient had a large pleural effusion and could not lie supine, but no obvious pericardial fluid or pericardial thickening could be demonstrated. A trans-esophageal echo cardiogram confirmed aortic sclerosis and no vegetations were noted, thereby excluding a large occlusive vegetation as a cause of the transient ST elevation. A coronary angiogram was performed which showed normal coronary arteries except for a small plaque in the proximal right coronary artery. Her ventriculogram was also

normal. The pleural effusion was drained with an intercostal drain and pleurodesis was effected with bleomycin. The patient was treated with diltiazem HCl 90 mg twice daily and aspirin, and she remained symptom-free at follow-up. Her subsequent chemotherapy included cyclophosphamide 1.2 g at 3-weekly intervals. Her disease once again responded entering complete remission. No adverse reaction was noted during these subsequent treatments.

Discussion

The above case report clearly fits with coronary vasospasm. The patient had transient, significant ST segment elevation with no enzyme leak and normal coronary arteries whilst she was receiving carboplatin. There is only one previous case report [1] of a patient with coronary vasospasm associated with carboplatin.

There are various invasive tests for eliciting coronary vasospasm. However, they carry a risk. Combination tests with intravenous ergonovine and, when ergonovine alone fails, intracoronary acetylcholine achieve higher rates of eliciting vasospasm, but ventricular tachycardia has been found in 2.5% of patients and atrial fibrillation in 5% of patients [2]. Noninvasive tests with hyperventilation and cold-pressor stress echocardiography have been performed, but sensitivity decreases from 91% with invasive tests to 48% [3]. Coronary vasospasm may produce focal organic lesions with the formation of neointima similar to that of restenosis. This may explain the small plaque observed in our patient's proximal right coronary artery [4]. The prognosis of patients with coronary vasospasm is excellent. Factors that predict poor outcome are decreased left ventricular function and diabetes [5].

This patient had a calcified aortic valve which was degenerative with a small nodule and mild incompetence of this valve. However, no mobile vegetations were seen prolapsing into the coronary ostium on trans-esophageal echo cardiogram, and therefore this aortic sclerosis or possible marantic endocarditis are unlikely to have been etiological factors. The large pleural effusion which was a complication of the ovarian cancer did not cause any respiratory decompensation, and the absence of pericardial fluid would suggest that the excess fluid noted in the cavity did not play a role in the pathogenesis of the documented coronary spasm. An association between cyclophosphamide and cardiac disease is well known, but it appears to be a dose-related phenomenon and there is disagreement as to whether cyclophosphamide at doses under 100 mg/kg per week contributes to cardiomyopathy. Higher doses used prior to bone marrow transplantation have been associated with hemorrhagic pancarditis [6, 7]. The $5HT_3$ antagonists used for chemotherapy-induced nausea have also been implicated in arrhythmias [8], but in our patient the $5HT_3$ antagonist was administered at least 1 h prior to the collapse.

Platinum salts were first observed to produce bronchial asthma among platinum refinery workers in 1945 [9]. Subsequent reports confirmed that platinum containing compounds could produce type I hypersensitivity reactions [10]. Thus, one would expect that, when used clinically, cisplatin and all its analogues would have the ability to cause hypersensitivity reactions. Cisplatin reactions have been reported in as many as 20% of patients in some series [11]. A reliable overall incidence has never been determined [12], but 5% or less is probably reasonable.

Analogues of cisplatin with nearly equivalent antitumor efficacy and lower rates of nephrotoxicity have been in wide clinical testing, and carboplatin is marketed and used in many cancers with good effect. Carboplatin has produced hypersensitivity reactions with approximately the same frequency as cisplatin (i.e. 2.5 to 10%). Two patients have been reported who had a type I hypersensitivity reaction to cisplatin and then developed a similar reaction to carboplatin [13, 14]. Calvert et al. [15] reported that a patient had reactions from repeated doses of carboplatin. Hypersensitivity to carboplatin is a rare but very real complication of therapy, and should be considered in patients presenting with hyperacute changes on ECG whilst receiving carboplatin therapy.

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