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Clinical insights into cisplatin-induced arrhythmia in a patient with locally advanced non-small cell lung cancer: a case report

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Abstract. – OBJECTIVE: Cardiotoxicity is a common adverse effect of many antineoplastic agents, including anthracyclines and paclitaxel. However, it has not been defined as a causal side effect of cisplatin. Here we report on a patient with locally advanced non-small cell lung cancer who developed a cardiotoxic event induced by cisplatin that manifested primarily as arrhythmia.

MATERIALS AND METHODS: Intensive cardiac monitoring through electrocardiogram was performed to estimate the severity degree and clinical condition of arrhythmia.

RESULTS: The frequency and severity of the arrhythmia had a strong temporal relationship with the administration of cisplatin, that made it likely that cisplatin was responsible for the cardiotoxicity observed.

CONCLUSIONS: In the present case report, we discuss the potential factors that may provide pivotal contributions to the patient's susceptibility to cardiotoxicity and review the published studies regarding the cardiotoxic influence of cisplatin. We also outline the critical points that oncologists should be aware of when dealing with such high-risk patients.

Key Words:
Lung cancer, Cisplatin, Cardiotoxicity, Arrhythmia, Cardio-oncology.

Case Presentation

A 69-year-old man with a history of tobacco cigarette smoking was admitted to our institution for left chest pain of five months' duration. The patient previously presented to hospital and was diagnosed, after a spectrum of cardiac examinations, with coronary atherosclerosis and premature ventricular contraction. He was treated with pharmacotherapy (atorvastatin calcium, aspirin enteric-coated and metoprolol tartrate tablet) to improve cardiac function and coronary circulation. However, this conventional treatment was ineffective as he continued to experience chest pain repeatedly. He was subsequently referred to our hospital for assessment. The outpatient contrast-enhanced computed tomography (CT) revealed a mass shadow located in the upper pulmonary lobe near the left hilum. Additionally, there were enlarged left hilum and mediastinal lymph nodes, chronic bronchitis, and emphysema (Figure 1A-1C). Four endobronchial ultrasound (EBUS) needle aspirates were performed to obtain a pathological diagnosis. However, these were not successful, and a transesophageal endoscopy was performed. This enabled detection of adenocarcinoma cells from the mediastinal mass. The patient was then diagnosed as having left lung adenocarcinoma with left hilar and mediastinal lymph node metastasis (cT2aN3M0, IIIB). Due to the inadequate biopsy samples, neither immunohistology nor gene detection could be performed. The patient was not eligible for surgery and so he was transferred to our lung cancer center for chemotherapy.

The patient's chest pain recurred before chemotherapy was commenced and a thorough examina-

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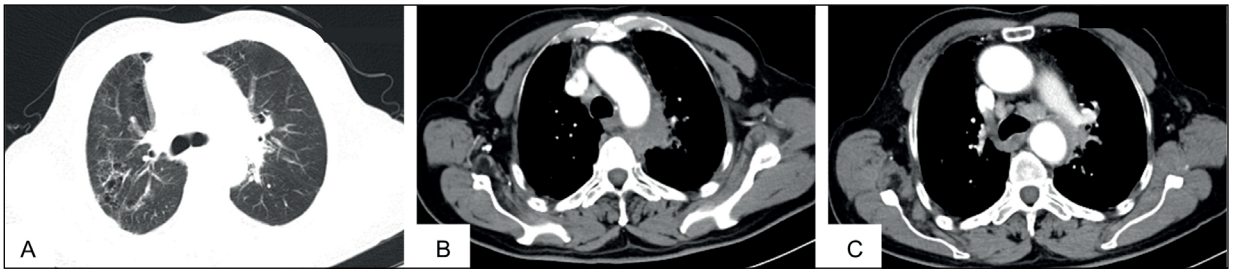

Figure 1. Representative clinical imaging findings at baseline. Chest contrast-enhanced computed tomography combined with thin-layer high-resolution scanning revealed (**A**) a soft tissue density mass lesion of approximately 2.7 × 4.2 cm near the hilum of the upper lobe of the left lung, encompassing (**B** and **C**) the thoracic aorta, the left pulmonary artery and the bronchus of the left upper lobe lung, with a fuzzy boundary and stenosis of the left upper lung bronchus. The mediastinal window was enlarged with slight enhancement of multiple lymph nodes in the left hilum and mediastinum.

tion was carried out including evaluation of heart function. An electrocardiogram (ECG) indicated sinus rhythm with premature ventricular contraction, while Troponin T (13.7 ng/L, reference value: 0-14 ng/L) and brain natriuretic peptide (39 pg/ml, reference value: 0-227 pg/ml) were within the normal limits. The ECG then returned to normal following initiation of a cardiologist's recommended treatment strategy aimed at anticoagulation, lipid-lowering and improving coronary blood flow (Figure 2A). A first-line chemotherapy regimen of intravenous pemetrexed (840 mg on day 1) and cisplatin (45 mg on day 1 followed by 40 mg on days 2 and 3) was commenced. There were no apparent adverse effects until the end of the first day of this first cycle when the patient complained of increased and persistent chest and back pain. Intensive cardiac monitoring displayed frequent ventricular premature systole without abnormal variations of heart rate (Figure 2B). Troponin T (13.7 ng/L) was negative, and brain natriuretic peptide (433 pg/ml) was slightly elevated. It was considered that his clinical signs may be cancer-related pain. Therefore, bucinnazine 100 mg was administered, resulting in symptom relief and in the decrease of premature ventricular detected by ECG monitoring. The chemotherapy was continued on the second day with no more overt cardiac or chest-related manifestations (Figure 2C). However, on the third day, the patient experienced another episode of chest discomfort during cisplatin infusion. ECG showed a heart rhythm of 40-70 beats per minute, premature ventricular contractions (bigeminy and trigeminy) and sinus bradycardia indicating gradual deterioration of sinus function (Figure 2D and 2E). Electrolytes, myocardial markers and blood pressure did not suggest any cardiac abnormalities. The cisplatin infusion was discontinued immediately, and the patient was observed. Overnight, the patient complained of more serious chest pain and was given another dose of bucinnazine, which resulted in symptom amelioration and normal sinus rhythm. An ECG was repeated the next day, with no evident sign of cardiac arrhythmia and no reappearance of chest discomfort (Figure 2F). Upon his second visit to hospital for chemotherapy, an ECG only showed rare premature ventricular contractions similar to those observed before his first chemotherapy. Given his last cardiac adverse event, single agent pemetrexed was utilized with no more ECG abnormalities detected.

Discussion

Cardiac toxicity is a well-known consequence of chemotherapeutic agents and biologicals, and is predominantly seen with anthracyclines, such as doxorubicin, epirubicin and daunorubicin[1]. Additionally, paclitaxel, 5-fluorouracil, methotrexate and targeted drugs (e.g., trastuzumab, bevacizumab and lapatinib) can also lead to myocardial damage[2]. Acute cardiotoxic reactions manifested mainly as sinus tachycardia, arrhythmia, conduction block, ST segment decline or flattened T waves, and are often reversible after drug withdrawal and symptomatic management. Delayed cardiac dysfunction is characterized by congestive heart failure and myocardial cell damage as well as by degeneration[3]. Pemetrexed plays its anticancer role by inhibiting multiple targets of the folate metabolic pathway. Cisplatin has a wide range of antineoplastic effects and is considered to be the foundation of double-chemotherapy for lung cancer. The most frequently observed toxicities of cisplatin involve the kidneys, nervous system, ears, bone marrow and gastrointestinal tract[4,5]. Both pemetrexed and cisplatin are considered to carry low risk of cardiac toxicity, which

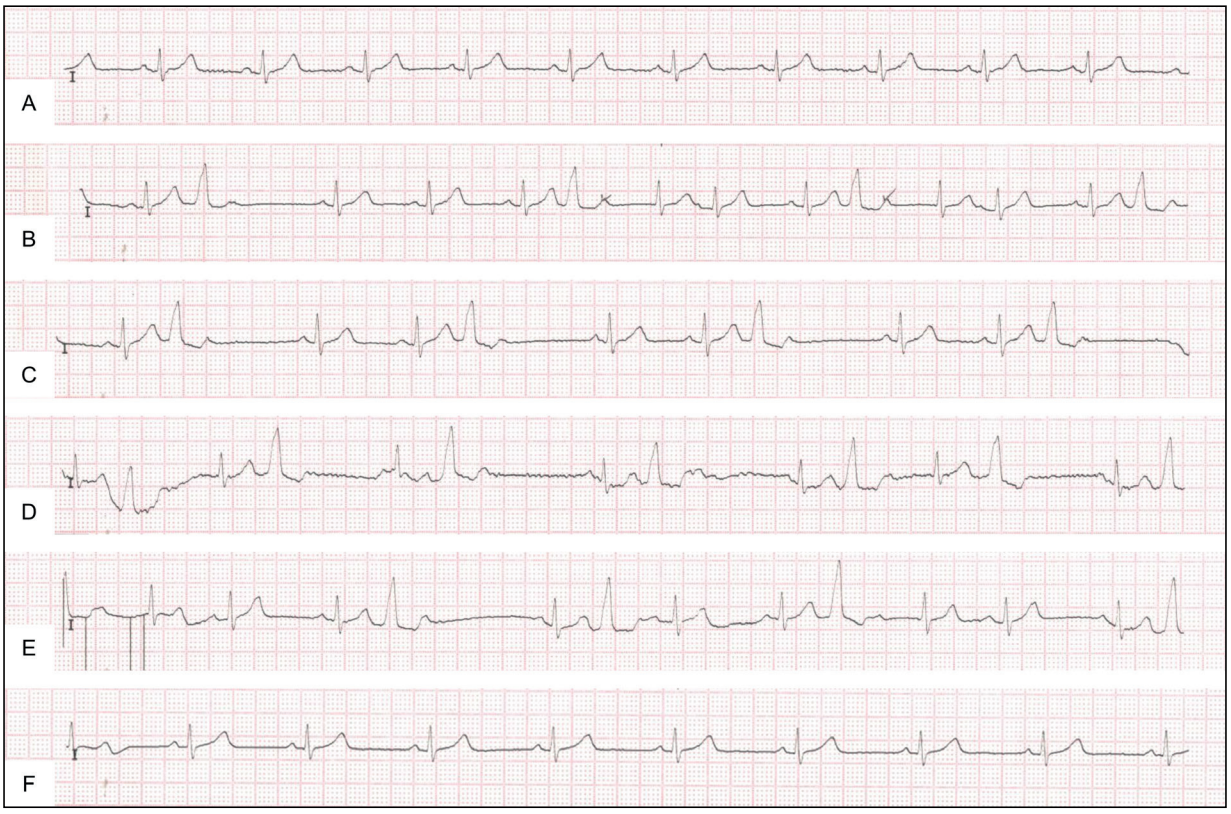

Figure 2. Dynamic electrocardiogram (ECG) changes before and during chemotherapy. ECG (**A**) before chemotherapy showed no apparent abnormality, whereas (**B**) arrhythmia was observed after administration of pemetrexed and cisplatin on the first day of the antitumor regimen, with the cardinal feature of premature ventricular contraction. After completion of the second day of cisplatin infusions, the ECG (**C**) displayed more severe ventricular premature beats and trigeminal rhythm followed by (**D** and **E**) a further deterioration of ventricular presystole immediately after the start of the cisplatin infusion the next day. This was manifested as bigeminy in association with sinus bradycardia, with a trend of gradual aggravation. Subsequently, the ECG (**F**) restored to sinus rhythm and no evident ventricular premature beats existed after cisplatin was discontinued and analgesic treatment was administered.

is part of the reason for choosing this regimen for our patient given his atherosclerotic heart disease.

Cardiac complications are not established side effects of cisplatin. However, in cases like ours it seems likely that cisplatin was responsible for the cardiotoxicity observed. First of all, the frequency and severity of arrhythmia closely related to the continuous administration of cisplatin. Secondly, the recovery of normal sinus rhythm was observed the day after the cisplatin infusion was discontinued. Third, compared with the first cycle, there were no newly observed arrhythmias and no deterioration in existing arrhythmias during the second cycle when cisplatin was the only discontinued agent. Collectively, this information clearly relates cardiac toxicity to cisplatin administration in this patient.

Cisplatin-based combinations have become one of the most widely used chemotherapeutic regimens since cisplatin's approval by the Food and Drug Administration in the United States of America in 1979. However, limited understanding of cisplatin-induced cardiotoxicity has been illustrated[6]. Over the past decade, a diverse range of cisplatin-related cardiac complications have been reported, such as angina, myocardial ischemia and heart failure[7,8]. Arrhythmia is the most commonly noted cardiac adverse effect appearing in the form of tachycardia with cisplatin[4,9]. Cardiotoxic effects caused by cisplatin may also manifest as bradycardia or asymptomatic arrhythmias, and mostly occur during or immediately after cisplatin infusion. These may sometimes be clinically important[2,4]. Since administration of cisplatin is generally not conducted under cardiac monitoring, asymptomatic bradycardia may not be noticed in clinical practice. Hence, the actual incidence of cardiotoxic events ascribed to cisplatin might be underestimated. The various possible mechanisms underpinning cisplatin-in-

duced cardiac dysfunction remain under investigation. Drug-induced damage to cardiomyocytes or blood vessels, the electrical conduction system, or the pericardium are possible underlying mechanisms according to existing studies[3]. Pathological mechanisms including induction of coronary vasospasm, damage of the vascular endothelium, oxidative and nitrosative stress, and electrolyte imbalance are frequently associated with acute complications, whereas cardiomyopathy may be the cause of late complications[2,3,8]. Moreover, it is published that cisplatin could accumulate in tissues such as the liver, skin and kidneys, and it may be detectable in blood 20 years after completion of a cisplatin infusion. This suggests the possibility that cisplatin could accumulate in the sinoatrial node and vessels causing long-term cardiotoxicity[8,10]. Although complex, cardiotoxic manifestations of cisplatin are a critical issue that warrant further clarification and identification of an appropriate solution.

In clinical practice, the possibility of cisplatin-induced cardiotoxic effects should be taken into account. Currently, it is recommended that the total cisplatin accumulation it is controlled to prevent high-risk drug exposure. Our patient had high sensitivity to cardiotoxicity as a result of his prior history of heart disease (coronary heart disease and arrhythmia), which made him more vulnerable to cardiotoxic drugs. Additionally, tumor metastasis to the hilar and mediastinal lymph nodes adjacent to the heart may partly explain the cause of cardiac symptoms such as chest pain and potentially complicate the differential diagnosis of the cardiac syndrome. As the patient experienced a decrease in the frequency of premature ventricular beats and relief of other arrhythmias after administration of an analgesic, it may be speculated that the arrhythmias might be at least partly due to cancer pain through stimulation of the sympathetic nerves. In patients, like ours, with risk factors for cardiotoxicity, it is prudent to utilize chemotherapeutic agents with potential cardiotoxic effects cautiously and to consider ECG monitoring during chemotherapy if use is unavoidable.

Conclusions

While platinum-based dual therapy is the cornerstone of chemotherapy for non-small cell lung cancer, cisplatin-induced cardiotoxicity should not be overlooked. Particular attention should be paid to patients with pre-existing cardiac disease and/or mediastinal tumors. It is important to evaluate cardiac function prior to chemotherapy and to consider cardiac monitoring during cisplatin infusions in susceptible patients. Furthermore, the use of potentially cardiotoxic concomitant medications (such as ondansetron and tricyclic antidepressants, which might induce QT interval prolongation) should ideally also be avoided[11]. Finally, resveratrol, acetyl-l-carnitine, DL-α-lipoic acid and silymarin may be used for protecting cardiomyocytes from cisplatin-induced cardiotoxicity[9].

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Conflict of Interest

The authors have no competing interests to declare.

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References

1) Darling HS. Cisplatin induced bradycardia. Int J Cardiol 2015; 182: 304-306.
2) Bovelli D, Plataniotis G, Roila F, ESMO Guidelines Working Group. Cardiotoxicity of chemotherapeutic agents and radiotherapy-related heart disease: ESMO Clinical Practice Guidelines. Ann Oncol 2010; 21 Suppl 5: v277-282.
3) Kucharz J, Michalowska-Kaczmarczyk A, Zygulska AL, Wojtak J, Pawlik W, Herman RM, Krzemieniecki K. Bradycardia as a rare symptom of cisplatin cardiotoxicity: A case report. Oncol Lett 2016; 11: 2297-2299.
4) Patanè S. Cardiotoxicity: cisplatin and long-term cancer survivors. Int J Cardiol 2014; 175: 201-202.

5) Oun R, Moussa YE, Wheate NJ. The side effects of platinum-based chemotherapy drugs: a review for chemists. Dalton Trans 2018; 47: 6645-6653.
6) Oun R, Rowan E. Cisplatin induced arrhythmia; electrolyte imbalance or disturbance of the SA node?. Eur J Pharmacol 2017; 811: 125-128.
7) Kounis NG, Cervellin G, Lippi G. Cisplatin-induced bradycardia: Cardiac toxicity or cardiac hypersensitivity and Kounis syndrome?. Int J Cardiol 2016; 202: 817-818.
8) Dugbartey GJ, Peppone LJ, de Graaf IA. An integrative view of cisplatin-induced renal and cardiac toxicities: Molecular mechanisms, current treatment challenges and potential protective measures. Toxicology 2016; 371: 58-66.
9) Raja W, Mir MH, Dar I, Banday MA, Ahmad I. Cisplatin induced paroxysmal supraventricular tachycardia. Indian J Med Paediatr Oncol 2013; 34: 330-332.
10) Gerl A, Schierl R. Urinary excretion of platinum in chemotherapy-treated long-term survivors of testicular cancer. Acta Oncol 2000; 39: 519-522.
11) Schlumbrecht MP, Hehr K. Cisplatin-induced bradycardia and the importance of the QT interval. J Oncol Pharm Pract 2015; 21: 157-160.