

Cisplatin-induced Atrioventricular Block Requiring a Pacemaker: Two Case Reports and a Literature Review

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Chemotherapeutic drugs can cause cardiac toxicities such as cardiomyopathy, arrhythmia, and cardiovascular disease. The well-known side effects of cisplatin are nephrotoxicity, nausea, vomiting, and electrolyte imbalance. Cardiotoxicity induced by cisplatin is rare, and its pathophysiology is unknown. Here, we present two cases of complete and high-degree atrioventricular (AV) block that occurred during cisplatin-based chemotherapy and required pacemaker placement. A 64-year-old woman and a 75-year-old man, who had no underlying heart disease, developed dyspnea without chest pain and bradycardia during cisplatin-based chemotherapy. However, there were no significant differences in their serum electrolyte levels, cardiac enzyme levels, and echocardiography results before and after drug administration. The ECGs were confirmed with complete AV block and high-degree AV block, which requiring pacemaker placement. We assume that cisplatin directly caused the complete, high-degree AV block, which required a pacemaker placement in our cases. In such cases, a cumulative dose of cisplatin over 240 mg/m² is a risk factor for early symptoms of AV block. If patients complain of dyspnea without chest pain during cisplatin-based chemotherapy, arrhythmic complications should be considered. This information may be helpful for clinicians treating patients with cisplatin chemotherapy.

Key Words: Cardiotoxicity, Cisplatin, Complete atrioventricular block

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INTRODUCTION

Complete atrioventricular (AV) block is a life-threatening arrhythmia that occurs when sinus impulses are completely blocked at the AV node. The causes of complete AV block include myocardial infarction, myocarditis, and medications such as anticancer drugs¹.

Cisplatin is a widely used alkylating chemotherapeutic agent. The well-known side effects of cisplatin are nephrotoxicity, nausea, vomiting, and electrolyte imbalance. However, cisplatin-induced cardiac toxicity is rare, especially in cases of AV block². Here, we have reported two cases of

complete, high-degree AV block that required a pacemaker placement during the course of cisplatin-based combination chemotherapy.

CASE REPORT

1. Case 1

A 64-year-old female patient had metastatic Klatskin's tumors and received a combination chemotherapy with cisplatin and gemcitabine at 3-week intervals. She had a history of diabetes mellitus and hypertension, but had no underlying cardiac disease. Her vital signs, serum electrolyte lev-

els, and ECG results were normal until the index event (Fig. 1A). The cancer was present only in the liver and peritoneal cavity. The patient suddenly developed dyspnea after the sixth cycle infusion of cisplatin (cumulative dose, 240 mg/m²). She showed bradycardia (heart rate, 38 beats per minute) such as typical symptom of complete AV block, without chest pain and fever. Her serum electrolyte, CRP, cardiac biochemical markers (troponin I and creatine kinase MB fraction), and glucose levels were within the normal limits. ECG revealed a complete AV block (Fig. 1B). Two-dimensional echocardiography revealed a normal left ventricular systolic function (ejection fraction, 71%) without a wall motion abnormality. The patient underwent a permanent pacemaker implantation due to irreversible persistent complete AV block, and the dyspnea was relieved. Follow-up ECG revealed good atrial sensing-ventricular pacing. Subsequently, the patient was administered a cisplatin-based chemotherapy again without any cardiovascular symptoms.

2. Case 2

A 75-year-old male patient with esophageal cancer underwent a combination chemotherapeutic regimen, including cisplatin and 5-fluorouracil. He had a history of hypertension, but had no cardiac disease and diabetes mellitus. The patient's vital signs, ECG, and serum electrolyte levels were normal at the start of chemotherapy, and the esophageal cancer had not invaded the heart. He was administered a cisplatin-based combination chemotherapy (cisplatin and docetaxel combination chemotherapy at 4-week intervals). He was admitted to the emergency department with general weakness after receiving the sixth cycle of the cisplatin-based chemotherapy (cumulative cisplatin dose, 315 mg/m²). He showed bradycardia (heart rate, 44 beats per minute) without chest pain and fever. His serum electrolyte, C-reactive protein (CRP), and cardiac enzyme levels were within the normal limits. ECG revealed a high-grade

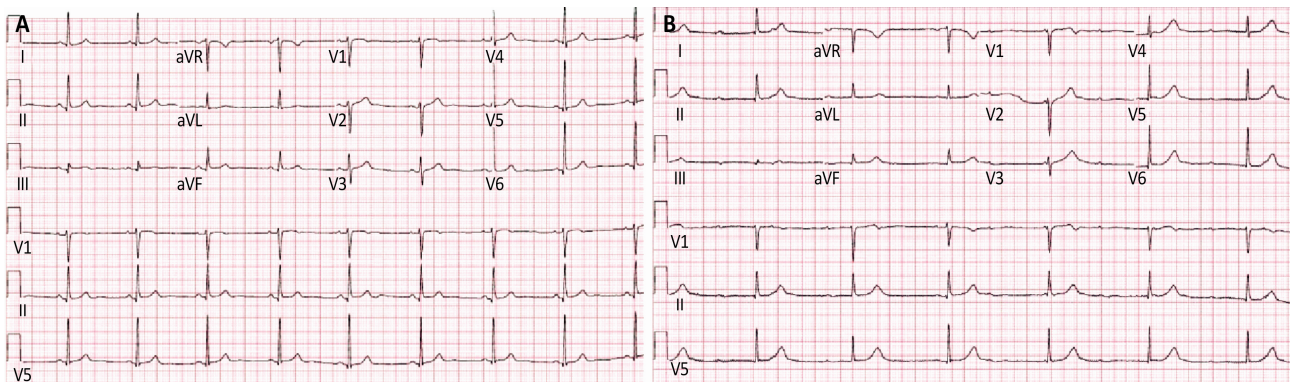


Fig. 1. Electrocardiography from Case 1. (A) Baseline ECG, (B) Complete Atrioventricular block.

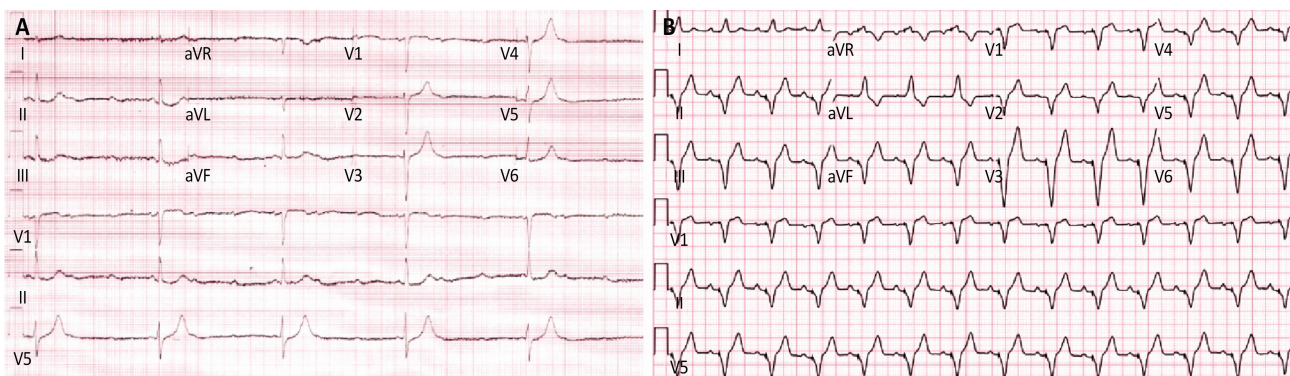


Fig. 2. Electrocardiography from Case 2. (A) High-grade Atrioventricular block, (B) Atrial sensing ventricular pacing ECG after implanting permanent pacemaker.

AV block without ST-segment elevation in the inferior leads (II, III, and aVF; Fig. 2A). Two-dimensional echocardiography was performed to exclude other heart diseases that can cause AV block. The left ventricular systolic function (ejection fraction, 73%) was normal without wall motion abnormality. A permanent pacemaker was implanted because the high-grade AV block was not reversible. After the pacemaker implantation, ECG results revealed good atrial sensing-ventricular pacing (Fig. 2B). The patient's general condition had improved, and he resumed the cisplatin-based chemotherapy with no cardiovascular symptoms.

DISCUSSION

Chemotherapeutic agents can induce various side effects, such as cardiotoxicity including heart failure, cardiovascular disease, and arrhythmia, which can lead to sudden death¹. For chemotherapy-induced cardiotoxicity, the mechanism of occurrence and reversibility of the cardiotoxicity depend on both the type of the drug and the patient's tolerability. Although the patient prognosis has improved recently, the sudden cardiac death caused by the cardiovascular complications of cancer treatment is still a major concern. Moreover, limited data are available for the early detection of cisplatin-induced cardiotoxicity and optimal oncological management.

Patients receiving cisplatin-based chemotherapy may experience coronary artery diseases, arrhythmias, and cardiomyopathy³. Moore et al. have reported cases of arterial thrombosis with subsequent myocardial infarction in patients who received cisplatin⁴. Arrhythmias can occur during the cisplatin-based chemotherapy and may result in supra-ventricular tachycardia (SVT), ventricular arrhythmias, atrial fibrillation, bradycardia, and complete AV block⁵⁻⁷.

Hypomagnesemia can be related to QT prolongation, which induces ventricular arrhythmias. Fiset et al. have reported cisplatin-induced hypomagnesemia with cardiac death in a rat model⁸. In a report by Pastorino et al., the kidney tubule damaged by within a few minutes of cisplatin generating hypomagnesemia and renal loss, which the patient's ECG revealed atrial fibrillation^{9,10}. In our cases, the patients had no underlying cardiac disease, and there were no significant changes in serum electrolyte levels. In con-

trast, a Turkish study showed that patients who received cisplatin-based chemotherapy presented silent arrhythmias, although most patients had no underlying cardiac disease and had normal serum cardiac enzyme and electrolyte levels¹¹. An electrophysiological study investigated the inotropic effect of cisplatin on the atria in an ex vivo rat model. Cisplatin administration significantly reduced the pacing rate in the right atrium without the force of contraction¹². On the basis of this study, we can infer that cisplatin can disrupt the electrical conduction system of the heart directly in terms of pathophysiology. Empirical studies^{13,14} have shown that oxidative cardiotoxicity mediates organ damage.

Taken together, the previous studies support the pathophysiological hypotheses that cisplatin-based chemotherapy affects arrhythmias in the following two different ways: 1) cisplatin-induced hypomagnesemia results in arrhythmia indirectly¹⁰ and 2) cisplatin causes arrhythmia directly¹². In the cases described in this report, the patients experienced dyspnea and general weakness, but there were no significant differences in their serum electrolyte levels, cardiac enzyme levels, and echocardiography results before and after drug administration. Therefore, we assume that cisplatin directly caused the complete, high-degree AV block, which required a pacemaker placement in our cases.

In our cases, the AV block developed during the course of cisplatin-based chemotherapy (cumulative cisplatin dose, 240-315 mg/m², not a single dose). If patients complain of dyspnea without chest pain during long-term cisplatin-based chemotherapy, arrhythmic complications should be considered, and we highly recommend an ECG.

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