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CASE REPORT

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Coronary vasospasm induced by cisplatin for seminoma

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Abstract

Vascular toxicity is one of serious complications following cisplatin-based chemotherapy. This case suggests that cisplatin has a potential risk of delayed occurrence of vasospastic angina. It is important to perform careful history taking including discontinued drugs for differential diagnosis of chest pain.

KEYWORDS

acetylcholine provocation test, chemotherapy, cisplatin, coronary vasospastic angina, onco-cardiology

1 | INTRODUCTION

A 34-year-old man, who had undergone surgical operation and chemotherapy including cisplatin for seminoma, was referred to our institution because of chest pain on exertion. Patient had exercise tolerance to be able to finish a race of triathlon for two years after chemotherapy. His coronary risk was only dyslipidemia, so we expected that possibility of organic stenosis was less likely. Since coronary angiography revealed no organic stenosis, acetylcholine provocation test was performed to rule out coronary vasospastic angina on exertion. Acetylcholine (50 μg) injection into coronary artery provoked severe coronary vasospasm accompanied with ST elevation in electrocardiography. Many paper reported that association between cisplatin and coronary artery disease. We speculated that his coronary spasm may be attributed to cisplatin toxicity although chemotherapy had been finished 2 years before the onset of chest pain.

Vascular toxicity is one of serious complications following cisplatin-based chemotherapy.[1,2] Early case reports suggested the association between cisplatin and coronary vasospasm.[3,4] Coronary vasospasm in those reports was diagnosed by transient ST segment elevation without organic coronary stenosis.[5,6] On the other hand, there were no studies or cases where coronary spasm was confirmed by acetylcholine provocation test. Here, we present a case of coronary vasospasm after cisplatin-based chemotherapy that was confirmed by acetylcholine provocation test.

2 | CASE REPORT

A 34-year-old man was referred to our institution because of chest pain on exertion. He had a history of seminoma whose TNM classification was $T_1N_2M_0$ (staged IIa) at the time of diagnosis. He had adjuvant chemotherapy for seminoma 2 years ago. The protocol of chemotherapy was combination of bleomycin, etoposide, and cisplatin, and total dose were 20 mg/m^2 (day 1-5), 100 mg/m^2 (day 1-5), and 30 mg/m^2 (day 1, 8, 15), respectively. Three courses of chemotherapy (every six months) after seminectomy were performed. He did not have smoking history. His coronary risk factor was only dyslipidemia. He had no chest symptom during and after chemotherapy. However, he began to feel chest pain two years after chemotherapy.

His height was 170 cm and body weight was 64 kg. Blood pressure was 110/75 mm Hg and heart rate was 65 per minute. Physical examination revealed normal heart sound without murmur, and no extremity edema in lower limbs. Electrocardiography at rest showed normal sinus rhythm without specific ST findings (Figure 1). Chest X-ray on admission was unremarkable. Cardiac biomarkers including

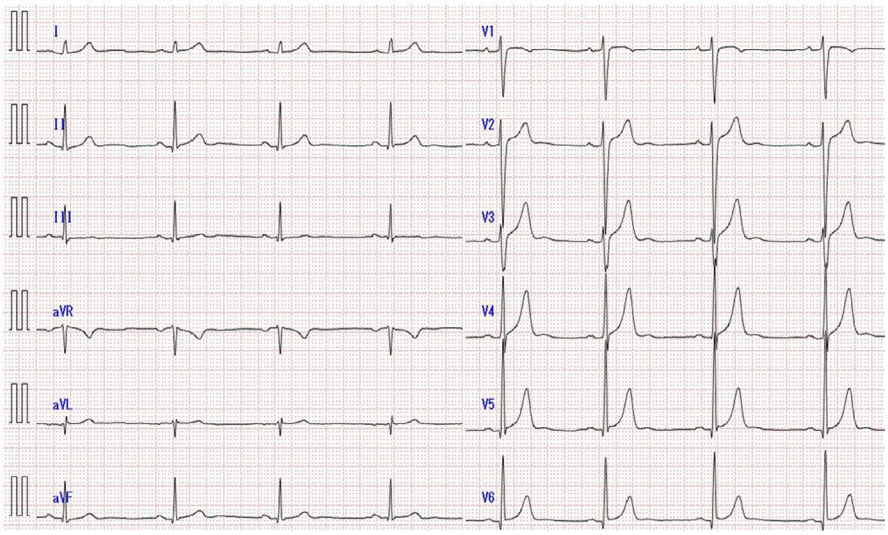

FIGURE 1 Electrocardiography on admission. There was no abnormal ST elevation in electrocardiography at rest

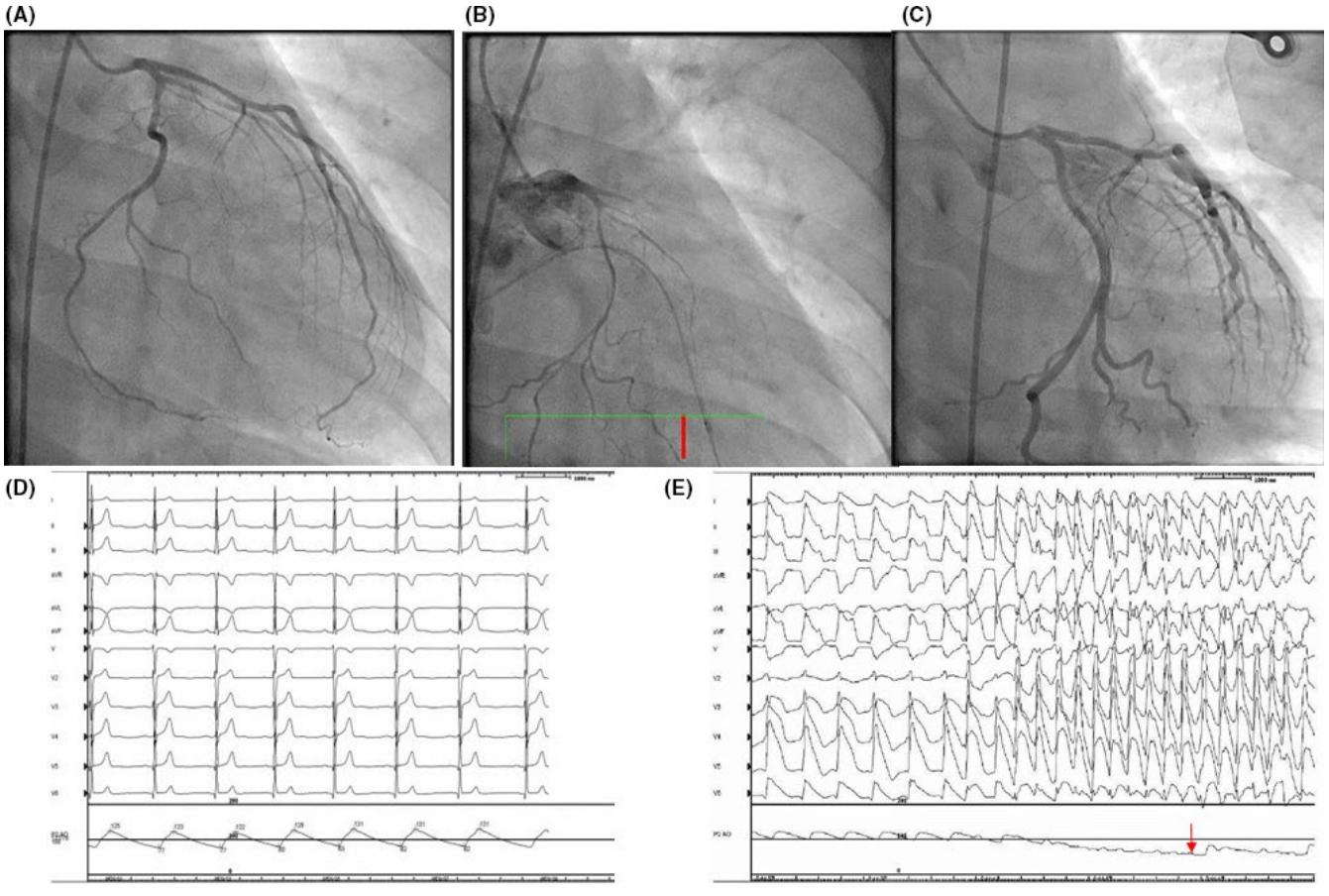

FIGURE 2 Coronary angiography and acetylcholine provocation test. (A) (upper column, left) Coronary angiography before acetylcholine infusion. There was not any organic stenosis in coronary artery, (B) (upper column, middle) after 50 μg of acetylcholine injection. (Catheter was not wedged position because left anterior descending artery was total occluded by severe coronary spasm.) (C) (upper column, right) After nitroglycerin. Dilatation of coronary artery by nitroglycerin was observed. (D) (lower column, left) electrocardiography and atrial pressure waveform before acetylcholine injection. There was no remarkable ST elevation. (E) (lower column, right) electrocardiography and atrial pressure waveform just after acetylcholine infusion, at same time as C. Remarkable ST elevation with severe chest pain was shown in II, III, aVF, and V_1-V_6 leads. Atrial pressure (red arrow) decreased gradually under 80 mm Hg

cardiac troponin I were not elevated. Total cholesterol was 223 mg/dL, and LDL cholesterol was 146 mg/dL. Serum creatinine was 0.86 mg/dL. eGFR was 83.2 mL/min/1.73 m^2. BNP was 5.1 pg/mL. baPWV(ba Pulse Wave Velocity) was right:1229 cm/s, left:1228 cm/s. Since coronary angiography (CAG) showed no organic stenosis (Figure 2A), acetylcholine provocation test was performed. Severe coronary vasospasm with total occlusion of the proximal segment of left ascending descending artery (LAD) was observed following intracoronary injection of acetylcholine (50 μg) (Figure 2B). He felt severe chest pain, and remarkable ST elevation in electrocardiography was recorded (Figure 2B,D). Coronary flow, chest pain and ST elevation in electrocardiography were promptly recovered just after the injection of nitroglycerin into the left coronary artery (Figure 2D). We diagnosed him as coronary vasospastic angina and prescribed benidipine hydrochloride 8 mg/d. His symptoms relieved after he received calcium channel blocker.

3 | DISCUSSION

This case report showed the association between history of cisplatin treatment and chest pain caused by coronary vasospasm. Although cisplatin treatment was discontinued 2 years ago before the onset of chest pain, coronary vasospasm was confirmed by acetylcholine provocation test. Our case suggests the importance of careful history taking including discontinued drugs for differential diagnosis of chest pain.

Early case reports revealed that cisplatin may cause acute myocardial infarction or coronary vasospasm.[5-7] Hanchate et al[6] reported a case which cisplatin-induced acute myocardial infarction and dyslipidemia. Fukuda et al[7] reported case series that vasospastic angina was likely caused by cisplatin-containing chemotherapy and thoracic irradiation for lung cancer. Acute vascular toxicity due to cisplatin can occur during or soon after chemotherapy and has been attributed to vasospastic angina.[8,9] However, previous reports diagnosed with vasospastic angina, because patients presented with chest pain, transient ST elevation in electrocardiography, and no organic stenosis by angiography.[5,6] Thus, there were no reports which proved coronary vasospasm by acetylcholine provocation test.

In the present report, control coronary angiography showed no organic stenosis, and acetylcholine provocation CAG revealed severe coronary vasospasm with strong chest pain and remarkable ST elevation. Cisplatin has possibility to cause coronary vasospasm after chemotherapy regimen for seminoma.[4] However, cisplatin was discontinued two years ago. The mechanism of this case was supposed that endothelial dysfunction was induced by cisplatin with time lag. Because this patient had dyslipidemia, persistent dyslipidemia and history of cisplatin might generate synergy effect for endothelial damage, which could induce coronary vasospasm.[6]

In the viewpoint of onco-cardiology, Hanchate reported that cisplatin vasculo-toxicity of endothelium in coronary artery is due to production of reactive oxygen species (ROS) which induce oxidative stress and are pro-thrombotic.[6] Ozkok reviewed that cisplatin and other platinum derivatives are the most widely used chemotherapeutic agents to treat solid tumors including ovarian, head and neck, and testicular germ cell tumors.[10] A known complication of cisplatin administration is acute kidney injury (AKI). The pathophysiology of cisplatin-induced AKI involves proximal tubular injury, oxidative stress, inflammation, and vascular injury in the kidney. Inhibition of the proinflammatory cytokines TNF-α or IL-33 or depletion of $CD4^+$ T cells or mast cells protects against cisplatin-induced AKI, and cisplatin also causes endothelial cell injury.[10] An understanding of the pathogenesis of cisplatin-induced endothelial cell injury is important for the development of adjunctive therapies to prevent coronary vasospasm, to lessen the need for dose decrease or drug withdrawal, and to lessen patient morbidity and mortality.

Our speculation has several limitations. First, we do not completely understand the risk factors for coronary vasospasm. In fact, coronary vasospasm often occurred without known risk factors. Second, we did not prove direct association between history of cisplatin and vasospastic angina. Moreover, it is still unknown why this patient did not have chest pain during chemotherapy.

In conclusion, our case suggests that cisplatin has a potential risk of delayed occurrence of vasospastic angina. It is important to perform careful history taking including discontinued drugs for differential diagnosis of chest pain.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTION

SM, HF: supervised this project. HW, KS, TI: revised the manuscript. JM, TH, HU: managed this patient. WS: wrote this paper. All authors approved the final version for publication and agreed to be accountable for all aspects of the work.

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REFERENCES

1. Kohn S, Fradis M, Ben-David J, Zidan J, Robinson E. Nephrotoxicity of combined treatment with cisplatin and gentamicin in the guinea pig: glomerular injury findings. *Ultrastruct Pathol*. 2002;26:371-382.
2. Herrmann J, Yang EH, Iliescu CA, et al. Vascular toxicities of cancer therapies: the old and the new–an evolving avenue. *Circulation*. 2016;133:1272-1289.

3. Borek G, Gebel F, Jenzer HR. Acute myocardial infarct following chemotherapy for testicular carcinoma: on the coronary toxicity of cytostatic agents. *Schweiz Med Wochenschr*. 1991;121:385-389.
4. Rodriguez J, Collazos J, Gallardo M, Hernando G. Angina pectoris following cisplatin, etoposide, and bleomycin in a patient with advanced testicular cancer. *Ann Pharmacother*. 1995;29:138-139.
5. Rao AS, Kumar R, Narayanan GS. A rare case of cisplatin-induced acute myocardial infarction in a patient receiving chemoradiation for lung cancer. *J Cancer Res Ther*. 2015;11:983-985.
6. Hanchate LP, Sharma SR, Madyalkar S. Cisplatin induced acute myocardial infarction and dyslipidemia. *J Clin Diagn Res*. 2017;11:OD05-OD07.
7. Fukuda M, Oka M, Itoh N, et al. Vasospastic angina likely related to cisplatin-containing chemotherapy and thoracic irradiation for lung cancer. *Intern Med*. 1999;38:436-438.
8. Atalik KE, Keles B, Uyar Y, Dundar MA, Oz M, Esen HH. Response to vasoconstrictor agents by detrusor smooth muscles from cisplatin-treated rats and antioxidant treatment. *Methods Find Exp Clin Pharmacol*. 2010;32:305-310.
9. Stefenelli T, Kuzmits R, Ulrich W, Glogar D. Acute vascular toxicity after combination chemotherapy with cisplatin, vinblastine, and bleomycin for testicular cancer. *Eur Heart J*. 1988;9:552-556.
10. Ozkok A, Edelstein CL. Pathophysiology of cisplatin-induced acute kidney injury. *Biomed Res Int*. 2014;2014:967826.

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