

Cisplatin-induced cardiotoxicity – two case reports

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ABSTRACT

Cisplatin has been used for over 40 years in various cancer chemotherapies. Toxicity induced by cisplatin-based therapeutic regimens include gastrointestinal toxicity, myelotoxicity, neurotoxicity, ototoxicity and nephrotoxicity. Cisplatin-based regimens have been associated with a wide range of cardiovascular complications. In this paper, we report 2 cases of cisplatin-induced cardiotoxicity.

We present cases of 2 young patients who developed acute myocardial infarction during combination chemotherapy with bleomycin, etoposide and cisplatin. The first patient had acute anterior wall ST elevation myocardial infarction and the second one had acute myocardial infarction with peripheral arterial thromboembolism.

Cisplatin use can result in cardiovascular events. Clinicians should be very cautious while managing patients on cisplatin-based chemotherapy. Early recognition of cardiotoxicity will allow for timely prevention of permanent cardiac damage.

KEY WORDS: cisplatin, cardiotoxicity, acute myocardial infarction, arterial and venous thromboembolic events

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INTRODUCTION

Cisplatin has been used for over 40 years in various cancer chemotherapies – it was first identified in 1960s [1, 2, 3]. It is a prototype from platinum group of antineoplastic drugs, which shows cure rates of nearly 90% in testicular cancers [4]. Cisplatin is also used in other cancers, including ovarian, cervical, small cell lung cancer as well as head and neck cancers [5]. The antitumor activity of cisplatin is associated with gastrointestinal toxicity, myelotoxicity, ototoxicity and neurotoxicity [1], and the chief, dose-limiting toxicity of cisplatin is nephrotoxicity [6]. Cisplatin-based regimens have been associated with a wide range of venous and arterial thromboembolic complications [6–16]. Arterial events are relatively less common than venous thromboembolic complications [11]. We report 2 cases of acute myocardial infarction after cisplatin-based chemotherapy.

CASE PRESENTATION

Case 1

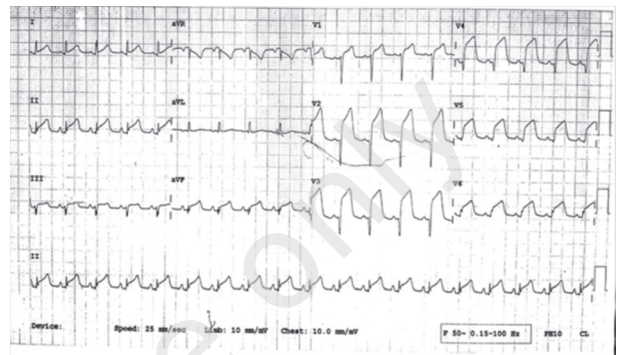
Mrs. X, a 27-year-old female from Bangladesh, presented with the following medical history: 2 months after second trimester abortion, patient underwent a laparotomy and myomectomy for a suspected uterine fibroid. The histopathological diagnosis was dysgerminoma. Baseline imaging showed no distant metastasis. The patient had no coronary risk factors and was scheduled for chemotherapy with two cycles of BEP regimen (bleomycin, etoposide, cisplatin) to be followed by surgery.

On the 8th day of the second cycle of BEP regimen, the patient presented to the emergency department with complaints of chest pain. She had an epigastric and anterior chest wall pain which was radiating to the jaw, occasional breathlessness on exertion and myalgia for one day. At the time of presentation, the heart rate was 110/min, blood pressure 160/110 mmHg, the chest was clear and the heart sounds were normal. ECG showed a J point and ST elevation in leads I, II, III, AVF and all lateral leads suggestive of acute extensive anterior wall and inferior wall ST elevation myocardial infarction (MI) (fig. 1).

The patient was immediately shifted to intensive care unit. 2D echocardiography (2D ECHO) showed left ventricular apical hypokinesis and left ventricular diastolic dysfunction, with left ventricular ejection fraction (LVEF) of 40–45%. Bedside troponin T card test was positive. The patient was thrombolysed with streptokinase and put on medications as per the standard acute coronary syndrome (ACS) protocol. There was symptomatic improvement; however, the patient developed hypotension which

FIGURE 1.

ECG at the time of presentation.



required pressor support on the 2nd day after admission to the ICU. Due to ECG showing persistent ST elevation, a coronary angiography was performed on the 3rd day, which showed total occlusion of distal LAD (fig. 2).

The patient was advised medical management and planned for observation with regular follow-up. Further cisplatin-based chemotherapy was withheld, as the risks of chemotherapy outweighed the benefits. The patient is currently asymptomatic and has been able to perform routine activities. Her follow-up 2D ECHO showed no regional wall motion abnormality; LV systolic function was normal. Although the etiology of the cardiac event in our patient is not clear, the lack of previous symptoms, absence of comorbidities, negative family history and the temporal link between the initiation of cisplatin-based chemotherapy and development of symptoms is suggestive of cisplatin-induced cardiotoxicity.

Case 2

Mr. Y, a 35-year-old male, presented with complaints of cough. A CT scan of the chest showed an anterior mediastinal mass, with bilateral lung nodules and liver lesions. β -hCG levels were at 1,000,000 mIU/ml. The histopathological diagnosis was choriocarcinoma. The patient had no comorbidities, was a non-addict with no significant family history. Baseline ECG showed sinus tachycardia (fig. 3). The patient was planned for chemotherapy.

In the 1st cycle, single agent chemotherapy with cisplatin 20 mg/m² (35 mg for 5 days) was started in view of deranged liver function tests. From the 2nd cycle, the patient received 75% of the dose of etoposide with cisplatin. Since the patient tolerated the chemotherapy well, he was given a full dose of etoposide in the 3rd cycle and was started on a full dose of the BEP regimen from the 4th cycle. However, due to increasing breathlessness, bleomycin was withheld from subsequent chemotherapy cycles.

FIGURE 2.
Coronary angiogram – schematic representation.

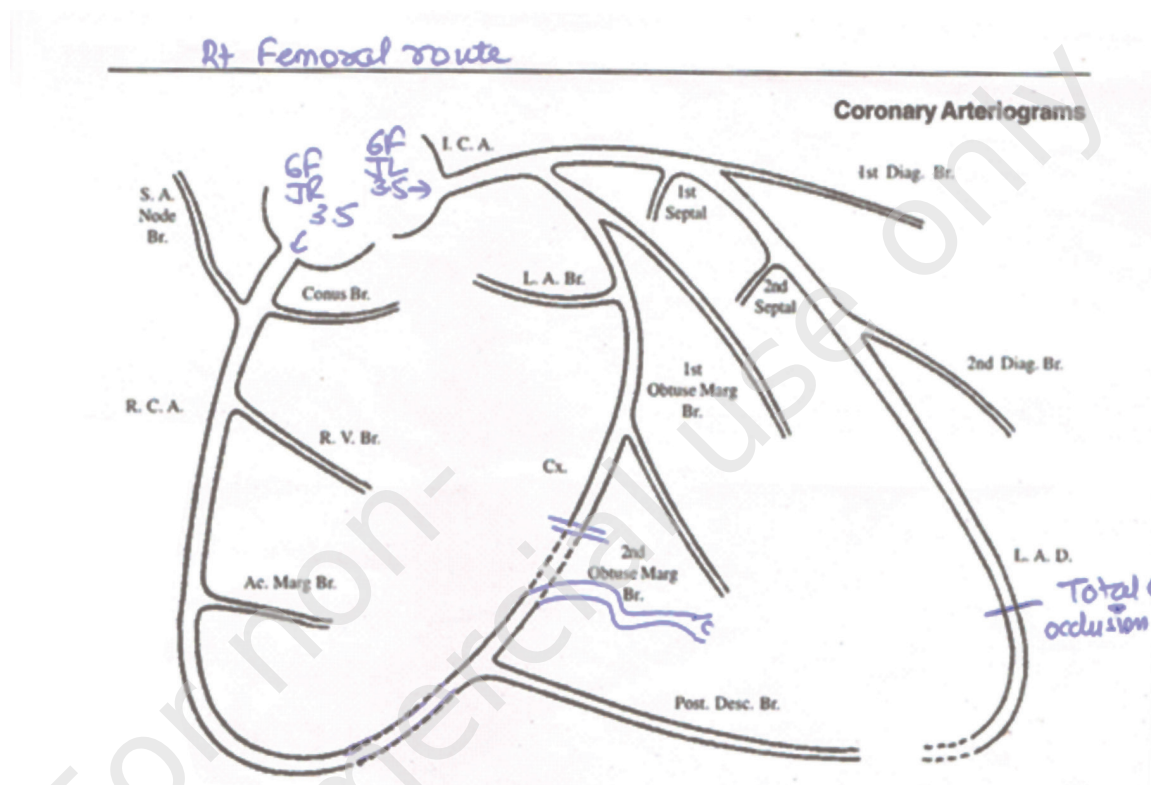
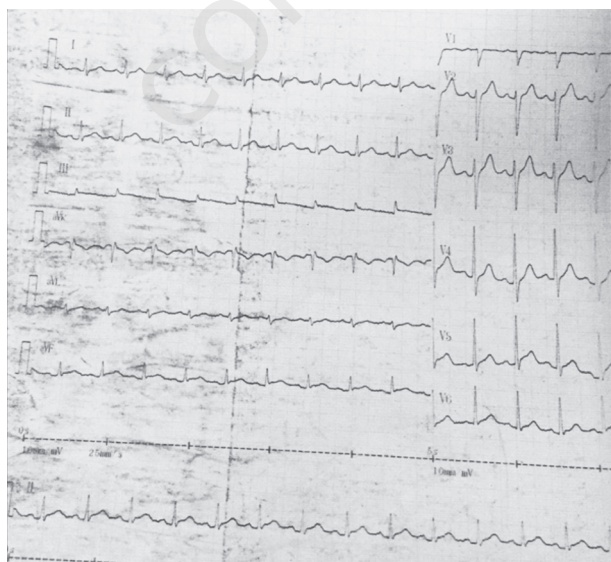


FIGURE 3.
Baseline ECG.

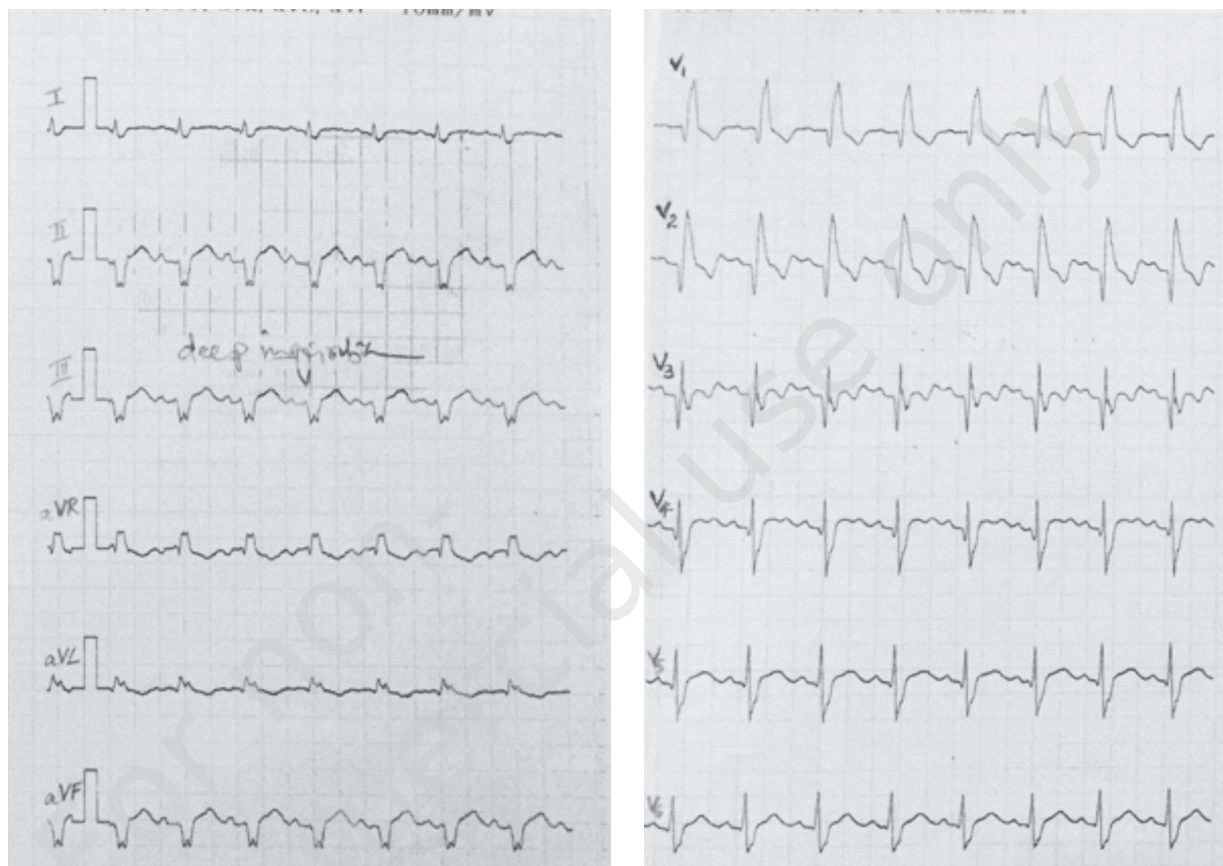


On day three of the 5th cycle of chemotherapy, the patient presented with complaints of dizziness with perspiration and breathlessness. At presentation, the heart rate was 120/min irregular, BP was at 90/66mmHg, the chest was clear and the heart sounds

were normal. ECG showed evolved ST elevation anterior wall MI with RBBB (fig. 4). 2D ECHO showed generalized hypokinesis of the entire LV with LV apical clot measuring 1.7 × 1.7 cm, left ventricular systolic dysfunction was present with LVEF of 20–25%.

The patient was shifted to ICU. In view of thrombocytopenia, anticoagulation was withheld. The rest of the treatment was given as per standard ACS protocol. On the 5th day following acute MI, the patient developed acute onset severe pain in the right lower limb. On examination, the right popliteal, anterior tibial, posterior tibial, and dorsalis pedis arterial pulses were not palpable. An emergency arterial doppler was performed, which revealed right arterial thrombus below femoral arteries with partial flow till anterior and posterior tibial arteries and partial thrombus in the right tibioperoneal trunk with 3 vessel distal runoff. However, no interventions were performed in view of thrombocytopenia (platelet count 30,000/μl). Once the platelet count normalized, the patient was started on low molecular weight heparin and overlapped with oral anticoagulant warfarin to achieve INR between 2 to 3.

FIGURE 4.
ECG showing evolved ST elevation anterior wall myocardial infarction with RBBB.



Second CT scan of the chest and abdomen was done for evaluation of response of the disease to chemotherapy. It showed interval regression in the size of the anterior mediastinal mass and bilateral pulmonary nodules. Serum β -hCG was at 1.4 mIU/ml, which indicated good disease control. Further chemotherapy was stopped. A follow-up CT scan of the chest performed 3 months later showed decrease in the size of the anterior mediastinal mass and no change in bilateral pulmonary nodules; β -hCG level was at 0.7 mIU/ml.

The patient is on regular cardiac follow-up and is currently asymptomatic. 2D ECHO done 6 months later showed hypokinesis of interventricular septum and left ventricular apical wall with LV systolic dysfunction and no LV apical clot; LVEF of 30–35%. Coronary angiogram was performed in May 2015, which revealed normal coronaries (fig. 5).

FIGURE 5.
Normal coronary angiogram.



DISCUSSION

Over the past few decades, there have been reports of cisplatin-associated cardiovascular toxicity manifested as both acute

reactions and delayed effects. Cisplatin has been reported to cause acute cardiotoxicity, like venous and arterial thrombosis, myocardial infarction, myocardial ischemia, myocarditis,

arrhythmias and diastolic heart failure [6–16]. Delayed cardiovascular effects, e.g. hypertension, dyslipidemia, increased body mass index, myocardial infarction and cerebral stroke have been documented [17]. Haugnes et al. studied the long-term risk of cardiovascular disease in survivors of testicular cancer. BEP had a 5.7-fold higher risk (95% CI: 1.9–17.1) of coronary artery disease compared with surgery only and a 3.1-fold higher risk (95% CI: 1.2–7.7) of myocardial infarction [17].

Czaykowski et al. reported 12.9% of vascular events in patients receiving cisplatin-based chemotherapy in a retrospective study of 271 patients treated with cisplatin; 77% of these adverse events occurred during the first 2 cycles of chemotherapy and 3 events led to death [18].

Moore et al. performed a large retrospective analysis of all patients treated with cisplatin-based chemotherapy. Among 932 patients, 169 of them (18.1%) experienced a thromboembolic event (TEE) during treatment or within 4 weeks of the last dose. TEEs included deep vein thrombosis (DVT) alone in 49.7% of the cases, pulmonary embolus (PE) alone in 25.4%, DVT plus PE in 13.6%, arterial TEE alone in 8.3%, or DVT plus arterial TEE in 3% [11].

The first patient reported here had the onset of symptoms on the 8th day of the 2nd cycle and the second patient presented with symptoms on the 3rd day after the 5th dose of cisplatin. The timing of the MI in relation to the start of the therapy further implies a relation between cisplatin and MI event. Previously reported myocardial infarction cases were observed 9 days after the completion of the 1st cycle to 18 months after the completion of 6 cycles of treatment [19]. In studies by Lee et al. and Moore et al., the cumulative dose of cisplatin did not correlate with TEE occurrence [11, 20]. A recent meta-analysis suggested that a bigger dose of cisplatin was associated with a higher risk of thromboembolism [21].

The mechanism behind the cisplatin-induced cardiovascular events is unclear. However, many hypotheses have been put forward. Several studies proposed that hypomagnesemia caused by cisplatin could lead to enhanced coagulation capacity and damage to vascular endothelial cells. Hypomagnesemia also results in increased intracellular concentration of calcium, ultimately leading to coronary vasospasm [22–24]. Some studies indicated an increase in von Willebrand factor levels leading to platelet adhesion and initiation of coagulation process in a big number of thromboembolic events [25]. Other factors, including Virchow's

triad, have been implicated in the possible mechanisms for myocardial infarction and thromboembolic events [26].

Many chemotherapeutic drugs other than cisplatin are involved in thromboembolic complications. A study by Haugnes et al. indicated that etoposide caused cardiovascular complications more frequently than cisplatin [17]. Oxidative stress on the myocytes and lipid peroxidation of cardiomyocyte membranes leading to permanent damage to the cell membrane structure and function have also been indicated as one possible cause of cardiotoxicity. This also explains the leakage of cardiac enzymes and markers like troponin I [27].

Our first case was a young woman with no coronary risk factors who presented with acute myocardial infarction. Her post-thrombolysis coronary angiogram revealed only a distal LAD block (probably a sludge), which suggested acute coronary thrombosis as the pathogenetic mechanism. Our second case was a young man with no known coronary risk factors who presented with acute myocardial infarction and later developed a peripheral arterial thrombosis. His coronary angiography was normal, which implied the possibility of coronary vasospasm due to cisplatin as a possible explanation. The lower limb arterial thrombus may have been caused by cardioembolism from LV apical clot or a de novo thrombosis due to cisplatin. Unfortunately, magnesium levels were not examined in our cases, although they should be monitored during chemotherapy with cisplatin. Patients on chemotherapy frequently present with symptoms of retrosternal burning. Regardless of the patient's age, the doctor should carefully watch out for symptoms of ACS when administering cisplatin-based therapy. In both cases presented in the article, these symptoms were promptly detected, which allowed for a timely intervention.

CONCLUSIONS

Patients receiving cisplatin-based regimen should be treated with a high degree of caution for cardiovascular events, because early recognition and appropriate treatment will prevent the morbidity and mortality associated with permanent damage. Many patients receiving BEP are young and usually do not have cardiovascular risk factors, so it may not be appropriate to advocate routine pretreatment cardiac stress test. However, patients with known coronary risk factors must be evaluated and optimized.

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Authors' contributions:

Sheela P. Sawant – idea & design of the article, writing the manuscript
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Anuprita D. Daddi – clinical data collection and analysis of the data
Jaya Ghosh – clinical data collection and analysis of the data
Amit Joshi – clinical data collection and analysis of the data
Aruna Alahari Dhir – idea & design of the article, writing the manuscript.