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Case Report

Oxaliplatin-induced acquired long QT syndrome with torsades de pointes and myocardial injury in a patient with dilated cardiomyopathy and rectal cancer

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Abstract

A 67-year-old woman presented with a history of dilated cardiomyopathy with congestive heart failure since 2003, who subsequently developed lower rectal cancer (adenocarcinoma) with liver, bone, and lymph node metastasis. Abdominoperineal resection and hepatectomy were performed. The patient received two rounds of intravenous chemotherapy, including 12 and six courses of FOLFOX4 (5-fluorouracil, leucovorin, and oxaliplatin; 85 mg/m^2 per cycle). She underwent a third round of intravenous FOLFOX4 because of tumor progression. During the 21st course of FOLFOX4 regimen, the patient developed ST segment depression in lead II and prolongation of QT interval with polymorphic ventricular tachycardia, torsades de pointes right after the start of oxaliplatin infusion. Immediate defibrillation and cardiopulmonary resuscitation were administered, and the patient regained spontaneous circulation and consciousness. Twelve-lead electrocardiogram showed ST segment elevation in III, aVF, and ST segment depression in V4–6 after resuscitation. To our knowledge, prolongation of QT interval with torsades de pointes and coronary spasm with myocardial injury that were stabilized in one patient following oxaliplatin infusion has not been reported. We present a patient with these rare complications.

Keywords: coronary vasospasm; hypersensitivity; long QT syndrome; oxaliplatin; torsades de pointes

1. Introduction

Oxaliplatin (Eloxatin; Sanofi-Synthelabo, New York, NY, USA) is the only third-generation platinum derivative routinely used in cancer therapy. It is particularly useful in the treatment of colorectal cancer. The acute toxicities of oxaliplatin include nausea, vomiting, diarrhea, neutropenia, thrombocytopenia, peripheral sensory neuropathy, and hypersensitivity reaction.[1] Hypersensitivity reactions to oxaliplatin vary from mild symptoms to severe anaphylactic shock, and may be life-threatening. The major manifestations of severe anaphylactic reaction include bronchospasm, tachycardia, hypertension or hypotension, and even cardiopulmonary arrest. Severe anaphylactic reaction and cardiac toxicity are rare, and the incidence increases when patients receive accumulated doses of oxaliplatin.[2] One case of oxaliplatin-induced coronary artery spasm with acute myocardial injury has been reported and associated with sensory neuropathy.[3] Oxaliplatin-induced long QT syndrome (LQTS) has been reported in a patient with appendiceal adenocarcinoma.[4] To our knowledge, prolongation of QT interval with torsades de pointes (TdP) and coronary spasm with

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myocardial injury exhibited in one patient following oxaliplatin infusion has not been reported. We report this rare complication in a patient with dilated cardiomyopathy and rectal cancer after prolonged use of oxaliplatin therapy.

2. Case report

A 67-year-old woman had dilated cardiomyopathy with congestive heart failure since February 2003, and subsequently developed lower rectum cancer with liver, bone, and lymph node metastasis (adenocarcinoma, T3N2M1, stage IV) in February 2007. Abdominoperineal resection and hepatectomy were performed, and she received 12 courses of the oxaliplatin regimen known as FOLFOX4 (5-fluorouracil, leucovorin, and oxaliplatin; 85 mg/m^2 per cycle). She underwent another six courses of FOLFOX4 plus Erbitux in 2010. Because of bone metastasis in the sacrum with severe bone pain, she received local radiotherapy and a third round of intravenous FOLFOX4 infusion for tumor progression in 2011. In April 2011, she was admitted for another course of FOLFOX4 therapy (a total of 21 courses). Upon admission, the 12-lead electrocardiogram (ECG) showed atrial fibrillation with rapid ventricular response, nonspecific ST-T change, and normal QT/QTc intervals (Fig. 1). However, the patient experienced tightness of the throat soon after the start of oxaliplatin infusion, as well as cold sweat and hypotension thereafter. On the ECG, there was a downsloping ST segment depression at lead II, prolonged QT/QTc interval of 480/628 milliseconds measured by an average of three sequential beats (Fig. 2A). Suddenly, the patient lost consciousness and exhibited no pulse. Her ECG monitor showed ventricular tachycardia, like TdP (Fig. 2B). Immediate defibrillation was carried out, using direct current shocks of asynchronized monophasic energy 300 J and cardiopulmonary resuscitation. Intravenous epinephrine bolus and dopamine infusion were also administered. The patient regained spontaneous circulation and consciousness. Twelve-lead ECG showed ST segment elevation in III, aVF, ST segment depression in V4−6, and prolonged QT/QTc interval of 320/459 milliseconds after resuscitation (Fig. 3). Electrolyte and cardiac enzyme levels were within normal limits: sodium 135 mmol/L (range: 135−147 mmol/L), potassium 4.10 mmol/L (range: 3.5−4.9 mmol/L), calcium 8.9 mg/dL (range: 8.5−10.5 mg/dL), magnesium 2.46 mg/dL (range: 1.6−2.6 mg/dL), CPK 54 IU/L (range: 38−174 IU/L), CK-MB 1.70 U/L (range: 3−10 U/L), and troponin-I 0.047 ng/mL (normal limit <0.5 ng/mL). Follow-up ECG showed a normal QT/QTc interval of 348/397 milliseconds on the 4th day after the patient's cardiac event. Cardiac catheterization showed normal coronary angiography, mild global hypokinesis of the left ventricle, and mild mitral regurgitation. The patient recovered from the side effects of oxaliplatin and was eventually discharged.

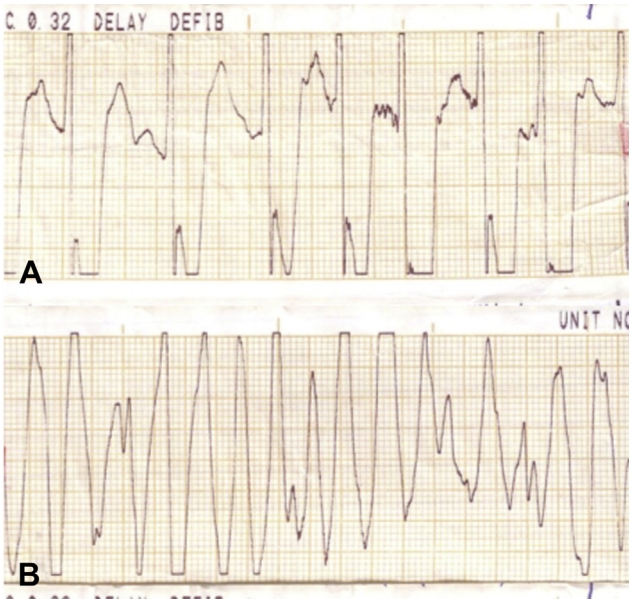

Fig. 2. Electrocardiographic recording (lead II) by monitor showed ST segment depression and prolonged QT/QTc interval of 480/628 milliseconds after (A) oxaliplatin infusion and (B) TdP polymorphic ventricular tachycardia.

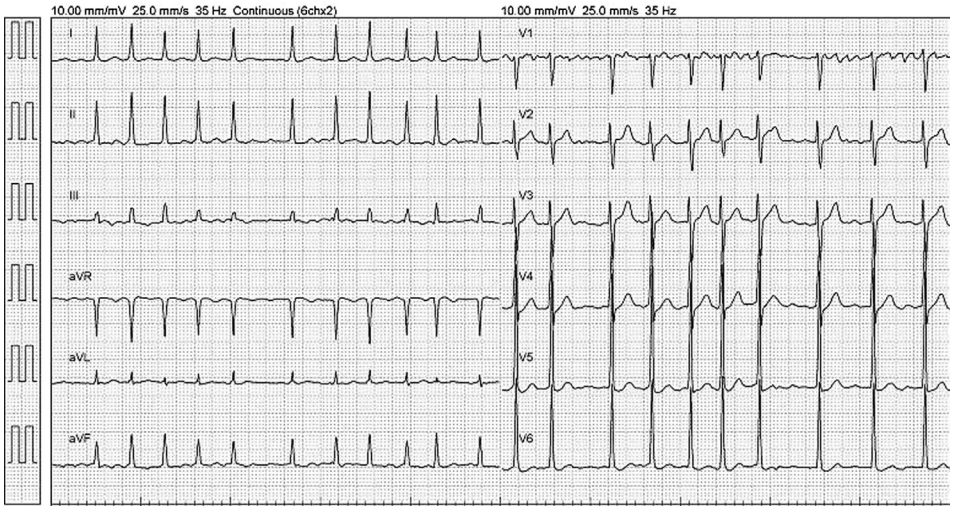

Fig. 1. Twelve-lead electrocardiogram (ECG) showed atrial fibrillation with rapid ventricular response, nonspecific ST-T change, QT interval of 300 milliseconds, and QTc interval of 370 milliseconds.

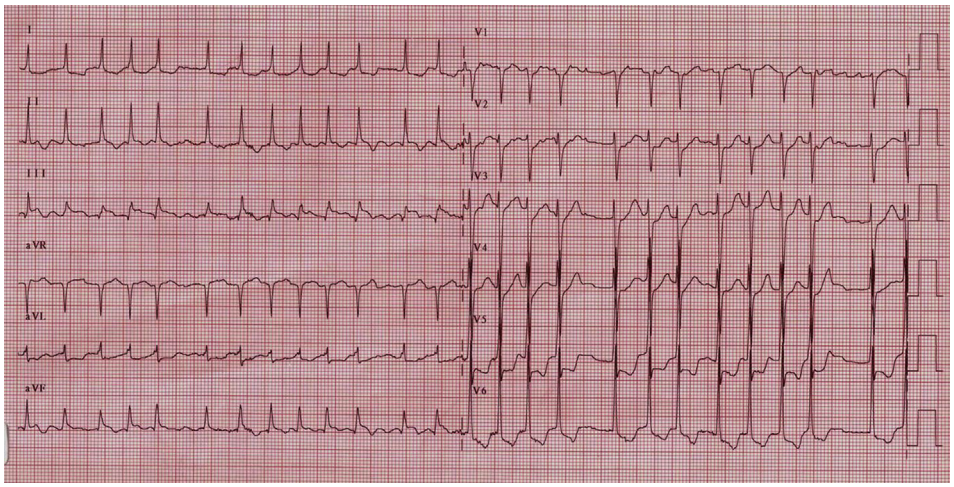

Fig. 3. Electrocardiography showed ST segment elevation over lead II, III, aVF, and ST segment depression, prolonged QT/QTc interval of 320/459 milliseconds over V4-6 after cardiopulmonary resuscitation.

3. Discussion

Allergic reactions to oxaliplatin vary, which can manifest mild to severe symptoms, and even life-threatening anaphylactic shock. Maindrault-Goebel et al[5] retrospectively analyzed the type and frequency of allergic reactions to oxaliplatin in 42 cancer patients. They reported type I immediate allergic reactions (respiratory in 47.6%, cutaneous in 40.5%, and anaphylactic shock in 3.1% of cases) and type II allergy (immunological thrombocytopenia in 3.1% of cases).[5] We previously reported severe anaphylactic reactions in 1.32% of patients receiving oxaliplatin therapy.[6] Anaphylaxis is immunoglobulin E mediated, and often rapid in its onset. Symptoms follow the release of potent chemical mediators from previously sensitized mast cells on antigen presentation.[7] The bridging of immunoglobulin E molecules attached to the mast cell surface activates an established pathway ending in mast cell granule release of histamine, heparin, and proteases, as well as the synthesis and secretion of leukotriene and prostaglandin mediators of anaphylaxis.[8] The direct vasoactive and smooth muscle spasmogenic effect of these mediators can cause coronary spasm. Coronary spasm in response to vasoconstrictor stimuli was observed in arterial segments with or without organic stenosis.[9] Most spasms were superimposed on fixed atherosclerotic lesions in 60% of the patients.[10] However, the occurrence of coronary spasm and myocardial injury precipitated by anaphylaxis in a patient with dilated cardiomyopathy and normal coronary angiography is rare.

In the present case, chest tightness and hypotension developed immediately after the 21st cycle of oxaliplatin infusion and was associated with ST segment downsloping depression in lead II and prolongation of QT interval. Moreover, this was followed by life-threatening arrhythmia. The proposed mechanism of hypotension and TdP is anaphylactic coronary spasm combined with oxaliplatin-induced QT prolongation, which is possibly due to the sodium channelopathy after cumulative doses.

Oxaliplatin is associated with several toxicities, the most common of which include nausea, vomiting, fatigue, diarrhea, neutropenia, and thrombocytopenia. Oxaliplatin accumulation is associated with its most characteristic and dose-limiting toxicity—sensory neuropathy. Oxaliplatin may also induce acute and chronic peripheral neuropathies. Acute peripheral neuropathy may be linked to the rapid chelation of calcium by the oxaliplatin metabolite oxalate and oxaliplatin-induced change in voltage-gated sodium channels through a pathway involving calcium ions.[11] A sodium channel is needed for impulse conduction by cardiac myocytes and cells of the His–Purkinje system.[12] The change in sodium channel kinetics may predispose oxaliplatin-treated patients to LQTS and TdP. The incidence of acute oxaliplatin-induced peripheral neuropathy is quite high, ranging from 65% to 98%.[13] However, cardiac toxicity of oxaliplatin has rarely been reported. QT prolongation following the 11th cycle of oxaliplatin infusion was reported in one patient who did not develop TdP. The predictors of TdP in drug-induced LQTS include a >0.28-second interval between the peak and end of the T-wave, T-wave alternans, increased beat-to-beat QT variability, and early afterdepolarizations.[14] Other risk factors for drug-induced LQTS include the female gender and hypokalemia.[15] Whether the accumulated dosage of oxaliplatin is related to cardiac toxicity warrants further study.

In conclusion, oxaliplatin is currently a cornerstone in the treatment of the early and late stage of colorectal cancer. Prolonged and repeated use of oxaliplatin in late-stage patients may induce sensory neuropathy. Cardiac toxicity manifested by anaphylaxis and prolongation of QT interval with TdP is potentially life-threatening. Consequently, clinicians should keep in mind risk factors that could lead to prolongation of QT interval and TdP in patients with cumulative doses of oxaliplatin therapy.

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