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Case Report

Takotsubo Cardiomyopathy After Oxaliplatin Chemotherapy Exposure: A Case Report

Shafaz Veettil, MD,[a] Omar Khan, MD,[a] and Daniel P. Durocher, MD[b]

[a] *Department of Medicine, Schulich School of Medicine and Dentistry, Western University, London, Ontario, Canada*

[b] *Division of Cardiology, Department of Medicine, Schulich School of Medicine and Dentistry, Western University, London, Ontario, Canada*

Oxaliplatin is a platinum-based chemotherapeutic agent employed in conjunction with either fluorouracil or capecitabine in treatment of advanced colorectal cancer. Takotsubo cardiomyopathy (TCM) represents a stress-induced ventricular dysfunction with regional wall-motion abnormalities not tied to a single coronary territory. Although fluorouracil and capecitabine have more well-documented associations with TCM, oxaliplatin's association is far rarer. We describe a patient with cecal adenocarcinoma who developed new-onset heart failure secondary to TCM, following oxaliplatin administration. This case is only the third such documented, and the first with a baseline echocardiogram for comparison. However, the incidence of oxaliplatin-induced TCM may be underrecognized in the literature.

Novel Teaching Points

- Oxaliplatin-associated TCM is described rarely, but so far, it has been demonstrated in women with gastrointestinal cancers who eventually achieved recovery of cardiac function after discontinuation of oxaliplatin treatment, and with supportive and/or medical management.
- TCM caused by oxaliplatin use should be considered in patients who have been identified as having fluorouracil-associated TCM, if they are exposed to both agents as part of their chemotherapeutic regimen. Distinguishing between the 2 etiologies may be difficult, as they seem to share similar clinical characteristics.

Case

A 69-year-old female patient who underwent right colectomy with resection of surrounding structures (appendix, fallopian tube, ovary, bladder dome) 4 months prior, for cecal adenocarcinoma, was initiated on oxaliplatin chemotherapy as part of a capecitabine–oxaliplatin (CAPOX) regimen, alongside capecitabine. At the time of oxaliplatin initiation, she had not received any doses of capecitabine. Her past medical history was notable for hypertension, dyslipidemia, asthma, celiac disease, and osteoporosis. She also had been an active cigarette smoker for > 45 years at the time of her presentation, and she had been taking only atorvastatin, 40 mg once daily, and inhaling fluticasone–salmeterol twice daily as needed. Twenty minutes prior to her first oxaliplatin infusion, she received single doses of oral dexamethasone, 12 mg, and oral ondansetron, 8 mg. She denied experiencing any recent significant emotional or physical stressors or use of over-the-counter or natural health products. Of note, 1 week prior to oxaliplatin administration, the patient underwent a transthoracic echocardiogram that demonstrated normal left-ventricular (LV) systolic function (ejection fraction of 60%-65%), with no regional wall-motion abnormalities.

During her oxaliplatin infusion (189 mg, intravenous, over 2 hours), the patient developed acute-onset dyspnea, respiratory distress, and a sensation of fullness in her chest. She initially was treated with diphenhydramine 50 mg intravenous and hydrocortisone 100 mg intravenous for a presumed allergic reaction. Although her symptoms improved somewhat initially, she presented to the hospital later that night after she once again developed severe dyspnea and light-headedness in bed. In the hospital, her high-sensitivity troponin-T level was initially 192 ng/L, and it was 206 ng/L 2 hours later. Her electrolyte panel and creatinine level were normal, and a complete blood count showed an elevated white blood–cell count, at 18.9 x 10^9/L, with zero eosinophils and a normal hemoglobin and platelet count. Her electrocardiograms (ECGs; Fig. 1, A and B) initially demonstrated slight ST-segment changes, which evolved to more-diffuse T-wave inversions.

She subsequently was admitted for urgent coronary angiography, which revealed no angiographic coronary artery disease. However, it did show decreased LV systolic function

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Corresponding author: Shafaz Veettil, Department of Medicine, Schulich School of Medicine and Dentistry, Western University, 800 Commissioners Rd E, London, Ontario N6A 5W9, Canada. Tel.: +1-519-685-8500 #16339.

E-mail: shafaz.veettil@lhsc.on.ca

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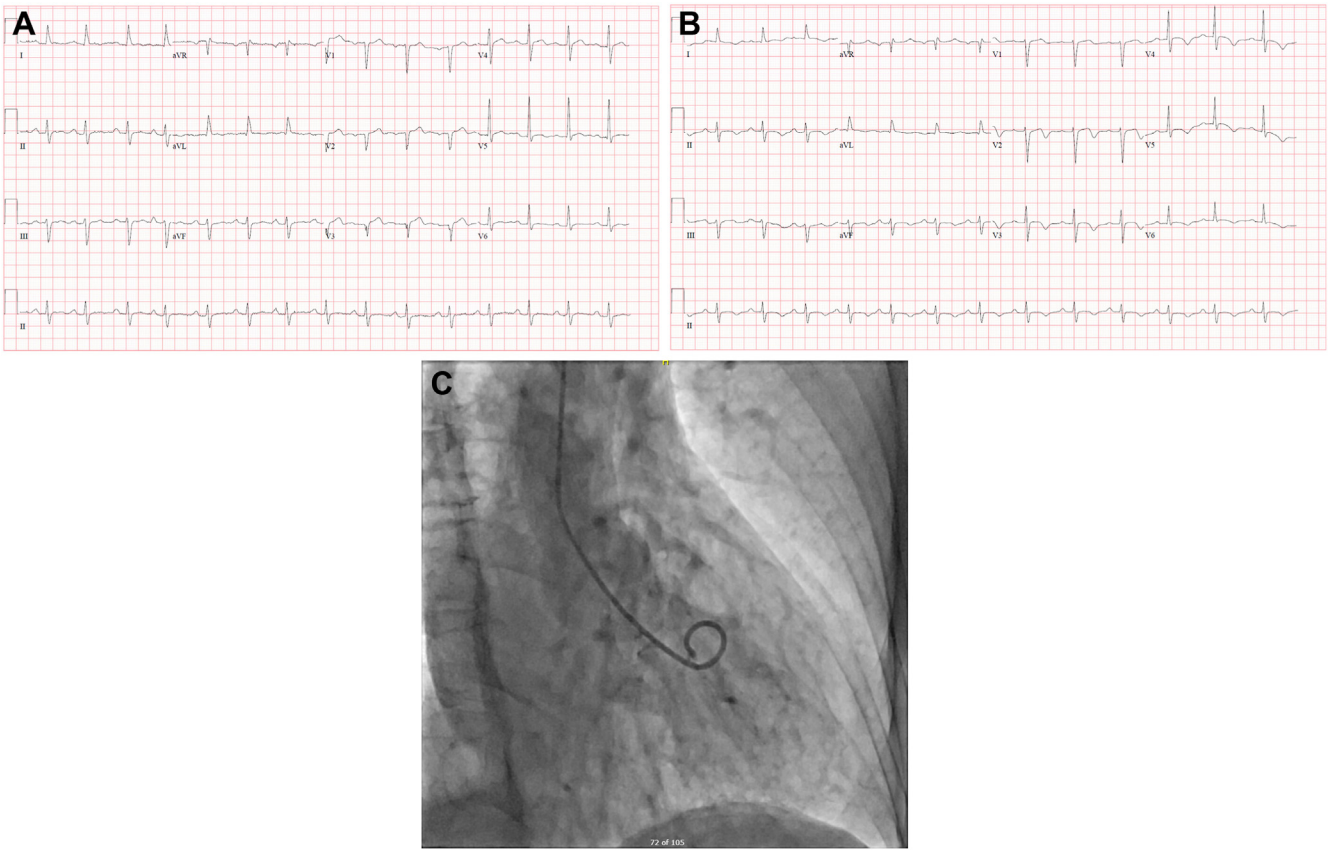

Figure 1. (**A**) Electrocardiogram on patient presentation showing subtle ST-segment elevations in leads V2—V4. (**B**) Subsequent electrocardiogram done approximately 12 hours later showing now-diffuse T-wave inversions. (**C**) Left-ventriculogram at end-systole during cardiac catheterization. The image demonstrates relative apical ballooning and appropriate basal segment contraction. aVR, augmented voltage right arm; aVL, augmented voltage left arm; aVF, augmented voltage foot.

with appropriate basilar segment contraction (Fig. 1C). Furthermore, an echocardiogram demonstrated an LV ejection fraction (EF) of 40%-45%, a stark contrast to her EF from her echocardiogram at the same institution 1 week prior. Moreover, in comparison, new hypokinesis of the mid to apical wall segments was also present, consistent with TCM.

The patient was managed supportively in the hospital and was discharged 2 days after her admission, in stable condition. An echocardiogram 2 months after discharge revealed mild improvement in her apical hypokinesis and in her LV EF to 45%-50%, after she had received medical therapy with bisoprolol. She is now being considered for raltitrexed chemotherapy by her oncology team.

Discussion

In this article, we present the third directly implicated case in the literature of TCM following oxaliplatin administration.[1-3] Here, oxaliplatin was the most likely the culprit behind our patient's presentation, with multiple historical factors supporting this causal link. First, the patient had not received any other chemotherapeutic agent by the time of oxaliplatin administration. Capecitabine treatment was due to start after the first dose of oxaliplatin, but it was held due to her hospitalization.

Second, her echocardiogram 1 week prior to the first dose of oxaliplatin showed normal LV systolic function, which argues against the influence of any baseline factor (eg, preexisting medications, such as atorvastatin) in her presentation. Her normal baseline echocardiogram strongly suggests that an intervening event in the following week led to the development of TCM; the event that most likely played that role was the administration of oxaliplatin.

Although our patient was treated initially as having an allergic reaction, her symptoms were limited to chest pain and dyspnea. She did not have any associated cutaneous or gastrointestinal symptoms, nor peripheral eosinophilia, to support an allergic etiology for the presentation. Given this context, our patient had a score of 5 points on the Naranjo Algorithm, indicating a probable causality between the use of oxaliplatin and her subsequent clinical distress.

We review 3 published cases of TCM associated with oxaliplatin use in Table 1.[1-3] Notably, Kim et al.[3] describe their patient's oxaliplatin and capecitabine treatments as potential etiologies for the TCM, but they do not directly implicate one agent over the other. However, with our patient, as well as with the patients of Coli et al.[1] and Osorio-Toro et al,[2] a clear link is present between oxaliplatin exposure and symptom onset.

In terms of demographics and past medical history, the sex and age range of the 3 cases identified in our literature search matches that of our patient, although our patient had relatively more cardiac risk factors.[1-3] All 4 patients had

Table 1. Previous case reports of oxaliplatin-associated Takotsubo cardiomyopathy

Characteristic	Coli et al.[1] (2015)	Osorio-Toro et al.[2] (2023)	Kim et al.[3] (2008)
Country	Italy	Colombia	United States of America
Patient information	67-year-old female patient with colonic cancer; previous surgery and now receiving XELOX	64-year-old female patient with stage IV gastric adenocarcinoma; receiving FLOT	75-year-old female patient with colonic cancer; current treatment with XELOX; treated previously with surgery, FOLFOX, and irinotecan plus cetuximab
Symptoms	Perioral dysesthesia, CP, dyspnea, hypotension at end of third session of oxaliplatin infusion	CP, diaphoresis, hypotension, bradycardia, and hypoxia during oxaliplatin infusion in cycle 6	Acute dyspnea after first chemotherapy session with oxaliplatin and capecitabine
Past cardiac history	Ex-smoker, normal baseline ECG	None reported	HTN and DLD
ECG changes	Mild transient STE in aVL lead and then diffuse TWI with QT-interval prolongation	STE in DI and aVL leads	New deep TWI in leads V2−V6
Troponin	Peak troponin-I level, 1.10 ng/mL	Troponin-I level, 75.71 Ug/L	Peak troponin-I level, 4.23 ng/mL
Coronary angiogram	< 50% stenosis in RCA; otherwise, normal coronary arteries	No significant lesions	Nonobstructive CAD
Echo and/or LV graphy	Mid-segmental akinesia with sparing of basal and apical areas	LV EF 47% on echo; anteroapical ballooning on LVgraphy with akinesis of inferolateral and anterolateral walls	LV EF of 35%-40%; akinetic anterior and anteroapical walls; severe inferoapical hypokinesis
Management	Chemotherapy held; initial medical therapy involving DAPT, statin, BB, ACE-i, and furosemide	Discontinuation of chemotherapy	Medical management with BB and ACE-i
Prognosis	Complete recovery of LV function on cardiac MRI 1 mo later	Recovery of cardiac function on cardiac MRI on day 7 of admission	Normal LV function with an EF of 59% on follow-up echo 2 wk later
Additional notes	Patient eventually restarted capecitabine with no further adverse events	Continued cancer treatment with pembrolizumab monotherapy	

ACE-i, angiotensin converting enzyme inhibitor; aVL, augmented vector left; BB, beta-blocker; CAD, coronary artery disease; CP, chest pain; DAPT, dual-antiplatelet therapy; DLD, dyslipidemia; ECG, electrocardiogram; echo, echocardiogram; EF, ejection fraction; FLOT, fluorouracil, leucovorin, oxaliplatin, and docetaxel chemotherapy; FOLFOX, folinic acid, fluorouracil, and oxaliplatin chemotherapy; HTN, hypertension; LV, left-ventricle; LV graphy, left ventriculography; MRI, magnetic resonance imaging; RCA, right coronary artery; STE, ST-segment elevation; TWI, T-wave inversion; XELOX (also known as CAPOX), capecitabine and oxaliplatin chemotherapy.

gastrointestinal cancer, and most of the cases presented with dyspnea and other extracardiac symptoms that initially were misattributed to an allergic reaction. Their investigations all were notable for troponin-level elevation, diffuse T-wave inversions and/or ST-segment elevation on ECG, lack of significant coronary artery disease on coronary angiogram, and subsequent improvement in cardiac function. Coli et al.'s[1] patient is notable for having a midventricular variant, whereas the other cases feature wall-motion abnormalities in the more-classical "apical" pattern of TCM.

A multitude of mechanisms have been proposed to explain the association between oxaliplatin use and TCM. Coli and colleagues,[1] for instance, postulated that oxaliplatin's neurotoxicity and ability to disrupt axonal ion channels could have resulted in TCM, via autonomic hyperexcitation and adrenergic overdrive. They also suggested that impaired intracellular calcium homeostasis caused by oxaliplatin and oxaliplatin-induced allergic coronary vasospasm were 2 other potential explanations for their patient's presentation. But they felt that the latter was not consistent with their patient's distribution of regional wall-motion abnormalities and symptoms. However, as noted by Madias,[4] the association with oxaliplatin use may be spurious. Instead, TCM in the setting of malignancy and the use of oxaliplatin, or other chemotherapeutic agents, could be a paraneoplastic manifestation of the underlying malignancy or could be due to the emotional and physical stressors associated with receiving a cancer diagnosis and undergoing cancer-related investigations and treatment.

Potential for unreported cases

Oxaliplatin is employed in conjunction with either fluorouracil or its oral prodrug capecitabine, in chemotherapeutic regimens used to treat colorectal cancer.[5] Fluorouracil-associated TCM is well documented and has been summarized in previous literature reviews.[6,7] Published cases explicitly identify fluorouracil as the agent responsible for TCM in their cases, despite the patients' potential recent exposure to oxaliplatin. Like the patients with oxaliplatin-associated TCM described in this current paper, patients tend to have no significant past cardiac history, with normal coronary arteries, predominance of dyspnea and other nonspecific symptoms as the presenting complaint, heterogenous ECG findings, normal coronary arteries, and an eventual complete recovery in cardiac function. Instances of patients requiring circulatory support for cardiogenic shock have been reported,[6,7] along with mixed success with reintroduction of fluorouracil chemotherapy.[6,7] Capecitabine use also has been implicated in TCM.[6]

We note that in the cases of fluorouracil-associated TCM described in the literature, oxaliplatin was not carefully considered as a culprit agent for TCM, despite patients having received both fluorouracil and oxaliplatin as part of their chemotherapy.[5,6] This lack of consideration likely was due to the lack of recognition in the published literature of oxaliplatin as a potential driver of TCM. Given the clinical similarities of these fluorouracil-associated TCM cases and the oxaliplatin-associated TCM cases described in this paper, some of the TCM cases that were attributed previously to fluorouracil could have been due to, or contributed to, by oxaliplatin exposure. The cases described by us, Coli et al.[1] and Osorio-Toro et al.[2] are all notable because they each describe patients treated recently only with oxaliplatin, and there is a clear temporal relationship between oxaliplatin exposure and symptom onset. However, in most other cases, patients often receive multiple agents over the course of a short period as part of chemotherapy, making the process of determining a primary culprit agent difficult.

Conclusion

We present a case of TCM characterized by a clear temporal relationship between oxaliplatin exposure with the onset of symptoms and new LV dysfunction. To our knowledge, and based on our literature review, this report is only the third one published in the medical literature that cites oxaliplatin-associated TCM, and it is the first to feature a baseline echocardiogram for comparison. Notably, our patient appears to share similar demographic and clinical features with the patients in the other reported cases. Future studies can help delineate the mechanism of this complication and increase recognition of oxaliplatin as a potential culprit in chemotherapy-induced TCM.

Ethics Statement

This research has adhered to the relevant ethical guidelines.

Patient Consent

The authors confirm that patient consent forms have been obtained for this article.

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Disclosures

The authors have no conflicts of interest to disclose.

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