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Case Report

Oxaliplatin-Associated Takotsubo Cardiomyopathy in a Patient with Metastatic Gastric Cancer: A Case Report

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Keywords
Oxaliplatin · Stomach neoplasms · Takotsubo cardiomyopathy

Abstract
We present the case of a 64-year-old female with stage IV gastric adenocarcinoma, pulmonary, and abdominal wall metastases, and no history of cardiovascular disease. In palliative care, she received systemic cytotoxic treatment with fluorouracil, leucovorin, oxaliplatin, and docetaxel protocol, which was well tolerated over five cycles. During cycle 6, she presented with cardiovascular symptoms with hemodynamic consequences while receiving oxaliplatin injection without docetaxel or 5-fluorouracil. She was transferred to the emergency department and then to the intensive care unit. She developed no complications during the hospital stay and was discharged after 10 days with preserved systolic function and no structural changes at the myocardial level. The electrocardiogram, echocardiogram, cardiac catheterization, and magnetic resonance imaging findings indicated an oxaliplatin-associated Takotsubo syndrome. The immunochemistry analysis showed PD-L1 expression level TPS: 40% and the foundation one genomic profiling revealed high mutation load, microsatellite instability, and HER2 not found. The patient is currently asymptomatic and on pembrolizumab monotherapy with good tolerance and partial treatment response.

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Introduction

Oxaliplatin is a platinum-based antineoplastic agent used for the treatment of colorectal, gastric, and pancreaticobiliary cancers [1]. This therapy can lead to side effects, such as diarrhea, vomiting, neutropenia, peripheral neuropathy, and – less frequently – anaphylactic reactions [2]. The chronic cardiotoxic effects of oxaliplatin have been commonly reported; however, the reports on its acute effects, such as complications that could lead to ventricular arrhythmias and sudden death, are few [3].

Several novel therapies have been approved for treatment of metastatic or advanced gastric cancer including HER2-targeted therapies (trastuzumab and trastuzumab deruxtecan) and Immune checkpoint inhibitors such as anti-PD1 (pembrolizumab) and anti-PDL-1 (nivolumab). Application of this therapy with and without chemotherapy shows clear benefits in response rates, time to progression, and overall survival [4–6]. However, the risk of early mortality should be considered in patients receiving management with immune checkpoint inhibitors [7]. Inflammatory microenvironment in gastric cancer can have an immune-modulatory function and may represent promising target for immunotherapy [6]. Nowadays, most molecular targeted therapies are under investigation for metastatic or advanced gastric cancer [4–6].

In this report, we present the case of a patient whose signs, symptoms, and imaging findings following the use of oxaliplatin were suggestive of Takotsubo syndrome; notably, this is a rare case reported in association with the use of 5-fluorouracil (5-FU) and capecitabine [8, 9]. This case report follows CARE guidelines. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000531389).

Case Presentation

A 64-year-old female patient with no history of chronic diseases or allergies was diagnosed with stage IV gastric adenocarcinoma because of pulmonary and abdominal wall metastatic involvement in January 2022. The patient received treatment with fluorouracil, leucovorin, oxaliplatin, and docetaxel protocol administered in cycles every 14 days, with good tolerance until cycle 5.

In cycle 6, during oxaliplatin infusion, the patient presented with oppressive chest pain, diaphoresis, hypotension (noninvasive blood pressure, 60/42 mm Hg), bradycardia (heart rate, 44 bpm), and desaturation (oxygen saturation, 72%; FiO_2, 21%). Accordingly, oxaliplatin administration was immediately discontinued, and she was transferred to the emergency department. She was initially managed with 0.9% sodium chloride and oxygen support by nasal cannula (FiO_2, 32%). On admission, an electrocardiogram (ECG) was obtained, and it revealed the evidence of ST-segment elevation in DI and aVL, suggesting acute myocardial infarction with ST elevation in the high lateral wall. Additionally, troponin l levels were elevated (75.71 [normal range, 0–40] Ug/L).

She was immediately examined by an interventional cardiologist who suggested emergency invasive coronary artery stratification. The results of the stratification revealed coronary arteries without angiographically significant lesions, with reduced left ventricular ejection fraction (LVEF) and anteroapical ballooning (Fig. 1, 2). Moreover, the transthoracic ECG image revealed concentric remodeling at the level of the left ventricle, akinesia with no thinning of the inferolateral wall and middle and apical segments of the anterolateral wall, and a slight deterioration in LVEF (47%).

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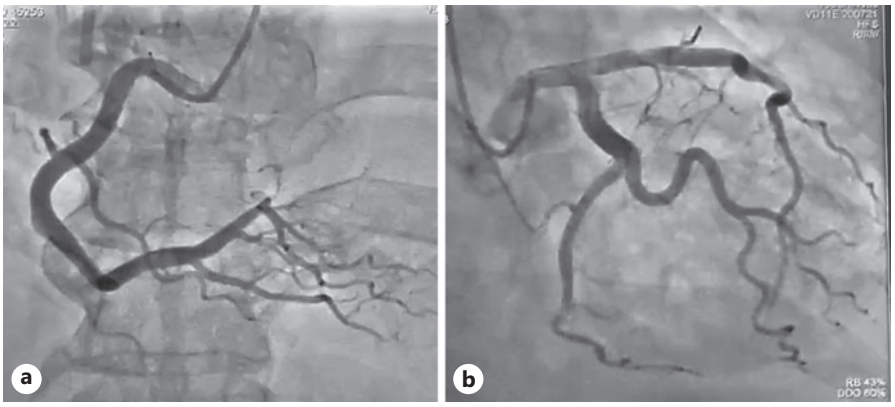

Fig. 1. Coronary angiography image. Coronary arteries with no angiographically significant lesions. **a** Right coronary artery. **b** Left coronary artery.

The patient was transferred to the intensive care unit for continuous cardiac monitoring. On the seventh day of hospitalization, cardiac magnetic resonance imaging was performed (Fig. 3); this revealed preserved systolic function with no valvular alterations and no signs of edema, fibrosis, or chronic inflammatory processes at the myocardial level.

During her hospitalization, she demonstrated a good clinical development, with no hemodynamic or respiratory deterioration; moreover, she did not develop any other cardiovascular complications. Therefore, she was discharged after 10 days of hospitalization.

Based on the abovementioned findings, including ST-segment elevation on ECG, positive troponins, echocardiographic changes in the left ventricle, cardiac catheterization with no evidence of macrovascular coronary artery disease, and subsequent recovery of cardiac function, the diagnosis of Takotsubo syndrome was confirmed. In addition, due to the lack of evidence of previous cardiovascular disease, it was concluded that Takotsubo syndrome was induced by oxaliplatin.

Considering the severity of the adverse reaction – classified as grade 4 at the cardiovascular level – to oxaliplatin, treatment with the fluorouracil, leucovorin, oxaliplatin, and docetaxel protocol was stopped, although the patient had achieved a partial response. Moreover, based on the findings of foundation one genomic profiling (Table 1) performed on gastric kerosene block, pembrolizumab monotherapy was continued.

Eight months after the occurrence of the adverse reaction, the patient is asymptomatic, has received twelve cycles of treatment with pembrolizumab at a dose of 200 mg every 3 weeks with good tolerance, has an eastern cooperative oncology group performance status of 0, shows partial response to treatment, and completes overall survival of 1 year. This report presents the latest transthoracic echocardiogram with preserved LVEF and no other relevant findings.

Discussion

In 2020, one million new cases of gastric cancer were reported worldwide, accounting for >760,000 deaths [10]. According to Globocan, in 2020, there were 8,214 new cases of gastric cancer with 6,451 deaths in Colombia, and gastric cancer was the fourth most common cancer in all age-groups in both sexes and the leading cause of cancer-related death [11]. Overall, 38–80% of patients with gastric cancer will present with metastatic or unresectable disease at diagnosis or develop metastatic disease over the course of the disease [12].

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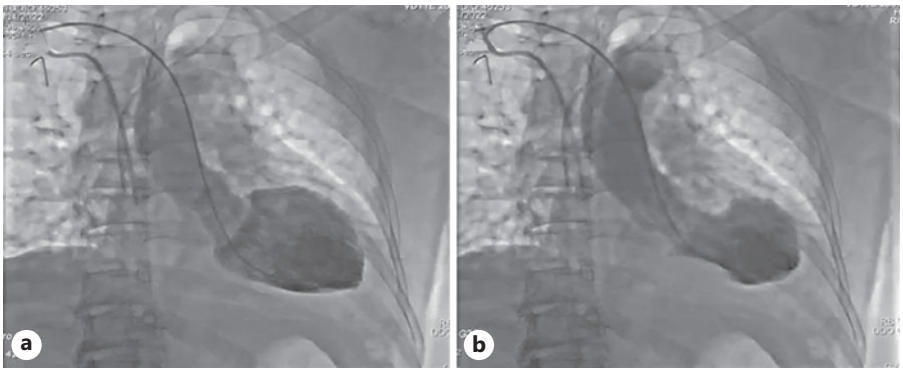

Fig. 2. Left ventriculography image. Anteroapical ballooning. **a** Telediastolic frame. **b** Telesystolic frame.

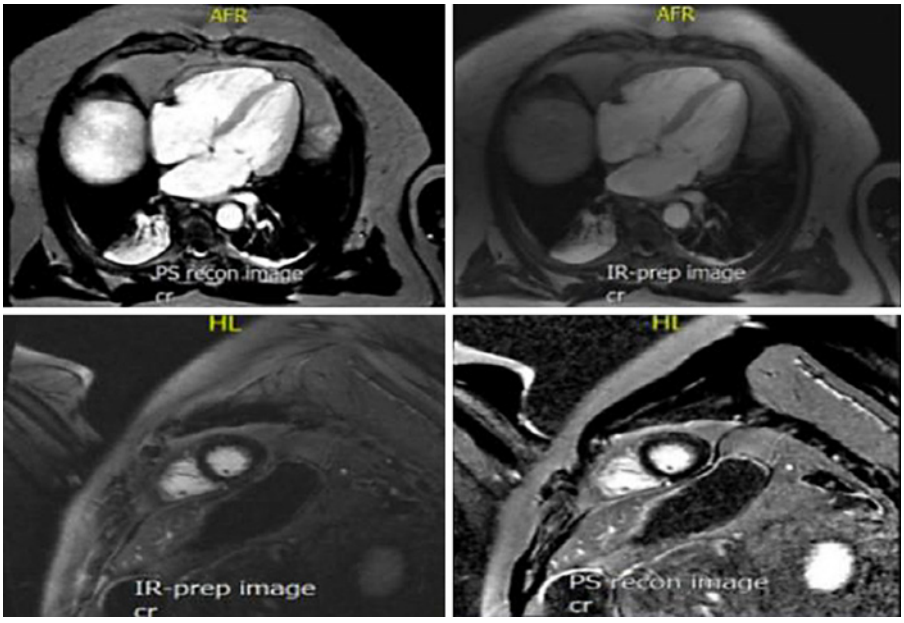

Fig. 3. Cardiac magnetic resonance imaging. No signs of edema, fibrosis, or chronic inflammatory process at the myocardial level.

Table 1. Foundation one profiling results: biomarkers findings

PD-L1 Combined-Positive Score (CPS)* 40
Microsatellite status (MSI) High
Tumor Mutational Burden-37 Muts/Mb
HER2 not found

We present a case of Takotsubo syndrome after oxaliplatin infusion in a patient with metastatic gastric adenocarcinoma (Fig. 4). To the best of our knowledge, this is a rare diagnosis in the literature, with only 2 case reports of colorectal cancer. The first case was reported by Jens Samol et al. [13] who clarified that it was a coronary spasm and the second was reported by Stefano Coli et al. [14], confirming Takotsubo syndrome.

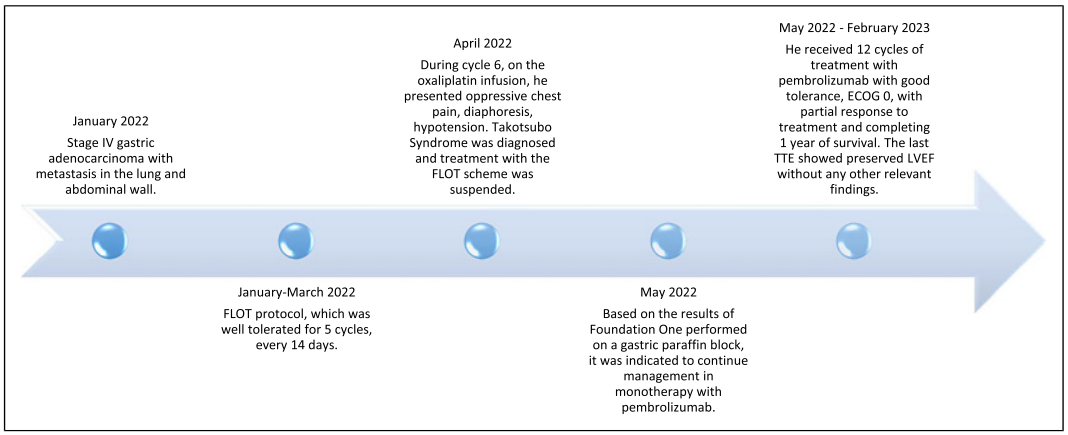

Fig. 4. Timeline of the main events of the case.

Acute cardiovascular effects are described in the literature, mainly with 5-FU and capecitabine [8, 9]. However, cases associated with electrocardiographic changes, such as ST and troponin 1 elevation, unstable angina pectoris, and acute myocardial infarction, have also been reported with rituximab [15], gemcitabine, and paclitaxel [16] use.

Cardiovascular effects associated with oxaliplatin are rare [17, 18]. Notably, in the present case, on the day the cardiac adverse event occurred, the only cytotoxic drug received in the infusion was oxaliplatin.

The possible pathophysiological mechanisms linking oxaliplatin to Takotsubo syndrome are cardiac adrenergic hyperstimulation and a chelating effect of oxaliplatin on calcium levels through its metabolite oxalate [14]. Other phenomena related to sodium and calcium channel dysfunction that may be related to cardiac changes have also been described [19, 20].

There are two main differential causes for ST-segment elevation in the present case. The first differential cause is Kounis syndrome [21], which manifests with coronary vasospasm during an allergic or hypersensitivity reaction. Because of the lack of allergic symptoms, such as rash, facial edema, or airway edema, this syndrome is considered unlikely in the present case. The second differential cause could be vasospastic angina, known as Prinzmetal's angina [22], which could be transient, and at the time of noninvasive stratification, manifests without vasospasm; this finding is similar to that observed in our patient.

Advances in personalized medicine have made it possible to provide patients with gastric cancer treatments with less toxicity and greater efficacy. This is an aggressive tumor with a poor prognosis as the median overall survival is between 3 and 5 months without treatment and approximately between 6 and 14 months with palliative chemotherapy [23].

Microsatellite instability occurs through the accumulation of errors in DNA microsatellites (short repetitive DNA sequences) caused by mutation or inactivation in genes encoding mismatch repair proteins (MLH1, MSH2, MSH6, and PMS2), with silencing of the MLH1 promoter [24]. This change has been described in 27 types of cancer including 22% of all gastric cancers [25] and 5% in metastatic gastric cancer [26].

Patients with high microsatellite instability metastatic gastroesophageal adenocarcinoma are chemotherapy-resistant and more likely to obtain durable responses to immunotherapy [27]. Fortunately, our patient met the three indications for immunotherapy: high mutational burden, microsatellite instability, and high burden mutational (Table 1). The benefit the pembrolizumab in this scenario has been validated in the KEYNOTE-158, KEYNOTE-059, KEYNOTE-061, and KEYNOTE-062 trials [28].

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With respect to the pharmacological treatment of Takotsubo syndrome, there are no randomized clinical trials; however, some retrospective studies have shown benefits regarding disease recurrence and mortality with the use of angiotensin II receptor blockers and antiplatelet both drugs used in our case [29]. It should also be borne in mind that the use of beta-blockers in this entity does not impact mortality, but they can play a particularly useful role because of their decreasing effect on catecholamine pathways, medication that was also used on the patient [30].

The decision to continue with pembrolizumab as monotherapy was made given that when a patient with advanced cancer receives palliative treatment, this should be focused on relieving symptoms, improving survival and quality of life, for this reason if dose-limiting toxicity is present, it is necessary to evaluate the causes and look for alternatives of directed treatment, safer, and more effective. Additionally, note that analysis by Chao et al. [31] indicated that both OS and PFS were prolonged in those receiving pembrolizumab monotherapy compared with chemotherapy and that pembrolizumab was more effective than chemotherapy in the setting first line.

It is expected that our patient will continue to receive pembrolizumab monotherapy without serious side effects and maintain clinical response and that she will achieve a complete response based on the results of the tumor genomic profile. The present case has several strengths within which it is possible to highlight the novelty of the case, the genomic study and the evidence of causality between the risk factor and the Takotsubo syndrome, however, as a case report it has the limitation that they cannot be generalized beyond the context of the informed patient.

Conclusion

This case report is significant because it highlights the need for careful patient monitoring during treatment infusion and the evaluation of cardiovascular risk factors because various anticancer drugs might cause acute cardiotoxicity. If ECG reveals ST elevation, the differential diagnosis should include acute myocardial infarction, coronary vasospasm, and Takotsubo syndrome. The timely and multidisciplinary management by invasive and noninvasive cardiology, internal medicine, clinical oncology, and critical care medicine is essential to achieve an accurate diagnostic and therapeutic approach to reduce morbidity and mortality in cancer patients with cardiovascular complications.

Although 5-FU is most commonly reported to cause Takotsubo syndrome, oxaliplatin should also be taken into consideration as a potential causative agent, as observed in the patient in this report. In addition, it is important to perform early genomic profiling of metastatic gastric cancer to find safer and more effective treatments than cytotoxic chemotherapy that significantly improve the quality of life and survival in pathology with high morbidity and mortality.

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Statement of Ethics

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. This study was approved by the Ethical Review Board of Clínica dew Occidente S.A. and its scientific committee (Act 01/2022).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Luis Miguel Osorio-Toro, Diana Marcela Bonilla-Bonilla, Santiago Leandro Escobar-Dávila, and Jhon Herney Quintana-Ospina: data collection, literature review, and writing the manuscript. Luis Álvaro Melo-Burbano, Edith Norela Benitez-Escobar, and Duván Arley Galindes-Casanova: data analysis and manuscript editing. Jorge Enrique Daza-Arana and Giovanna Patricia Rivas-Tafurt: editing and approved the final manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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