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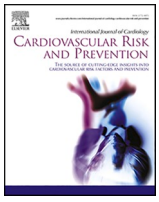

Takotsubo syndrome as an acute cardiac complication following combined chemotherapy

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ABSTRACT

Background: Acute cardiac complications post-chemotherapy is rare. Stress cardiomyopathy, one of these complications, should be considered in differential diagnoses as its symptoms closely resemble those of acute myocardial infarction and can lead to mortality.
Objective: The objective of this paper is to describe Takotsubo syndrome (TTS) as an acute complication following combined chemotherapy in a patient with significant thromboembolic burden and metastatic cervical cancer.
Case: A 61-year-old female patient with a diagnosis of metastatic cervical cancer experienced acute chest pain. Elevated troponin levels and abnormalities in the electrocardiogram initially suggested an acute myocardial infarction, occurring after a chemotherapy session involving Carboplatin and Paclitaxel infusion. Although initial treatment targeted myocardial infarction, further diagnostic evaluations including coronary angiography and cardiac magnetic resonance imaging revealed no coronary artery disease but identified features consistent with stress cardiomyopathy, indicative of Takotsubo syndrome (TTS). This diagnosis led to an improvement in symptoms and a resolution of the acute changes observed.
Conclusion: Stress cardiomyopathy, particularly TTS, is being increasingly recognized as an acute complication associated with combined chemotherapy regimens. The potential cardiotoxic effects of these chemotherapy agents demand careful monitoring and evaluation in patients undergoing oncological treatment, underscoring the importance of integrating cardioprotective strategies into the management of these patients.

1. Introduction

Chemotherapy is one of the mainstays of treatment in cancer patients, given its evidence in reducing mortality and increasing survival rates. Along with its benefits, it brings potential toxicity to various organs, including the heart [1]. This toxicity depends not only on the drug but also on the dosage, cycles, schedule, administration route, and patient-specific factors such as age and comorbidities [2]. Within the spectrum of complications, Takotsubo syndrome (TTS), or "broken heart syndrome," is an uncommon yet significant complication, with many aspects still remaining elusive [3]. First described in Japan in 1990 by Dr. Sato, TTS is a form of non-ischemic cardiomyopathy identified by the dilation of the left ventricle of the heart, leading to acute heart failure following an emotional or physical stressful trigger, transient in nature and occurring in the absence of coronary obstruction [4]. Its clinical presentation is typical, with chest pain in up to 82 % of cases and dyspnea in up to 50 %, and a mortality rate approaching 28 % in patients experiencing cardiogenic shock [5]. The pathophysiology of TTS is not fully understood, but it is thought to involve coronary artery vasospasm, excess catecholamines, microvascular dysfunction, and a genetic component. The relationship between TTS and oncological pathology has been attributed to physical and emotional stress, inflammatory status, and specific neoplastic mediators [6]. Additionally, drugs used in oncologic treatment such as 5-fluorouracil (5-FU), immune checkpoint inhibitors (ICIs), and vascular endothelial growth factor inhibitors (VEGFi) have been identified as playing key roles [7]. Among chemotherapeutics, the paclitaxel-carboplatin combination is employed for treating various types of cancer. Although still unclear, several

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mechanisms linking these drugs to TTS have been proposed. Concerning paclitaxel and taxanes, they can precipitate a hypersensitivity reaction with massive histamine release and subsequent alteration of the cardiac conduction system. Concurrently, an increase in the production of reactive oxygen species among cardiomyocytes has been suggested, leading to the collapse of the mitochondrial membrane for both paclitaxel and carboplatin [8,9].

We report an acute reaction to a combined chemotherapy infusion with carboplatin and paclitaxel in a patient with stage IV cervical cancer.

1.1. Case presentation

We report the case of a 61-year-old woman with no familial cardiovascular disease history, yet with a personal history of arterial hypertension. She was diagnosed with stage IV cervical cancer, exhibiting metastases to the liver, peritoneum, pleura, lungs, and adnexa. Additionally, she presented with venous thrombosis spanning from the external iliac vein to the inferior vena cava, accompanied by subacute to chronic thromboembolism. The patient presented to the emergency room of a primary care center with oppressive chest pain at rest, rated 8/10 on the Visual Analog Scale (VAS), radiating to the neck and jaw that started 2 hours after completing the third cycle of chemotherapy with Carboplatin and Paclitaxel. The admission ECG showed ST-segment elevation from V2 to V6 and negative T waves (Fig. 1). Blood tests indicated elevated cardiac biomarkers (Troponin) and anemia with normal volumes (Table 1). Consequently, the patient was presumed to have ST-elevation myocardial infarction (STEMI) and was given antiplatelet therapy with acetylsalicylic acid and clopidogrel, then referred to a more complex center for coronary angiography.

Upon admission, the patient had tachycardia and precordial pain. Coronary angiography revealed no obstructive lesions (Fig. 2-A), raising suspicions of myocardial infarction with non-obstructive coronary arteries (MINOCA), versus Takotsubo cardiomyopathy (stress). Cardiac magnetic resonance imaging (MRI) was then performed, revealing a normal sized left ventricle (LV) (average end-diastolic diameter of 50 mm) and signs of moderate eccentric hypertrophy (left ventricular mass index calculated at 120 g/m2). Marked hypokinesia of the apical and midventricular segments was noted. An ejection fraction of 38.3 % and a cardiac output of 4.87 l/min were observed, with no evidence of intracavitary thrombus, left atrial masses, or other significant findings. T2-weighted images showed minimal enhancement in the middle of the septum and part of the anterolateral wall, compatible with myocardial edema. Additionally, a slight delay in subendocardial perfusion of the antero-apical septum was observed, with homogeneous enhancement of the myocardium at the end of the first-pass perfusion. No early or late enhancements suggesting scarring, fibrosis, or an inflammatory process were present post-contrast injection.

Treatment was initiated with Carvedilol 6.25 mg every 12 hours, Enalapril 5 mg every 12 hours, Dapagliflozin 10 mg once daily, and anticoagulation with enoxaparin. Additionally, chemotherapy was discontinued, and a follow-up echocardiogram was scheduled in 4 weeks on an outpatient basis. During the follow-up visit, normalization of the

Table 1
Comparative Blood Analysis on Patient's Admission. This table presents the patient's blood test results upon admission, juxtaposing the patient values against standard reference ranges and providing a subsequent analysis of whether these values fall within normal parameters.

Parameters	Patient Value	Reference Range	Analysis
White Blood Cells (WBC)	5.7 × 10^3/uL	5–10 × 10^3/uL	Normal
Neutrophils	5.1 × 10^3/uL	2.2–4.8 × 10^3/uL	Abnormal
Lymphocytes	0.37 × 10^3/uL	1.1–3.2 × 10^3/uL	Abnormal
Hemoglobin	10 g/dL	12–16 g/dL	Abnormal
Hematocrit	38 %	40–51 %	Abnormal
Mean Corpuscular Volume (MCV)	77 fL	80-94 fL	Abnormal
Platelets	331 × 10^3/uL	150–500 × 10^3/uL	Normal
Creatinine	0.9 mg/dL	0.5–0.95 mg/dL	Normal
Blood Urea Nitrogen (BUN)	25.5 mg/dL	6–20 mg/dL	Abnormal
AST (Aspartate Aminotransferase)	21 U/L	0–40 U/L	Normal
ALT (Alanine Aminotransferase)	10 U/L	0–41 U/L	Normal
Troponin	0.824 ng/mL	0–0.014 ng/mL	Abnormal
Potassium	3.75 meq/L	3.5–4.5 meq/L	Normal

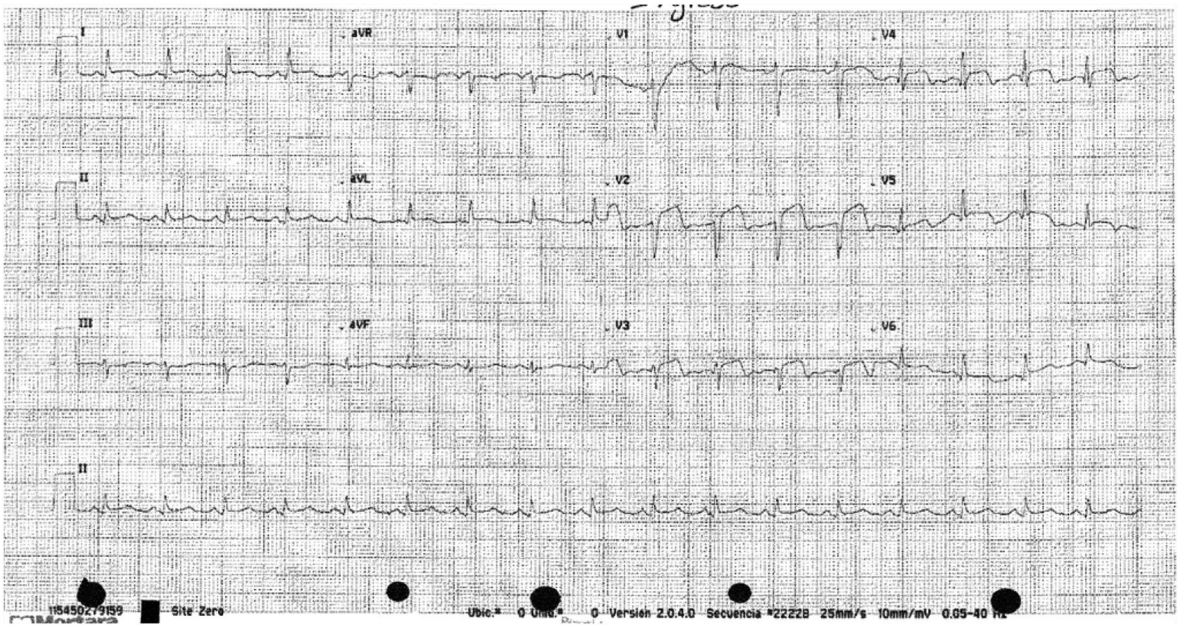

Fig. 1. Admission electrocardiogram (EKG) of patient. This figure displays the patient's ECG upon admission, illustrating ST-segment elevation in leads V2 to V6 and negative T waves. These findings are indicative of significant cardiac stress, characteristic of Takotsubo Cardiomyopathy. The ECG pattern is crucial for differentiating Takotsubo from other acute cardiac events, especially in patients with complex medical profiles.

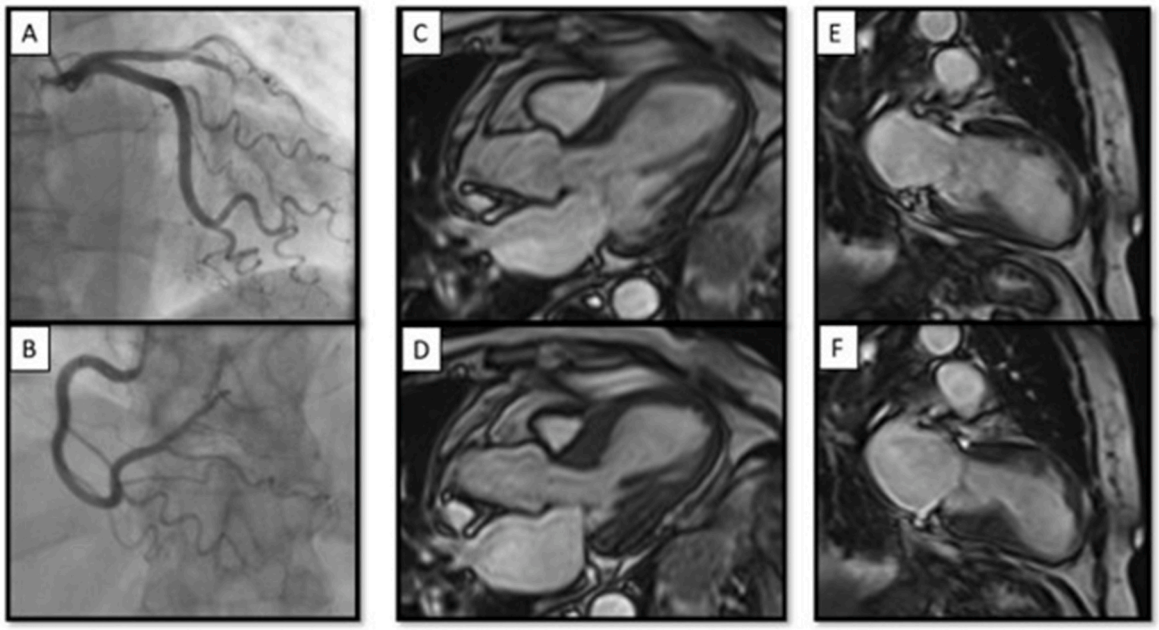

Fig. 2. Diagnostic Imaging Series for Cardiac Evaluation A: Left coronary artery with TIMI Flow Grade 3. B: Right coronary artery with TIMI Flow Grade 3. C: Cardiac magnetic resonance imaging, 4-chamber cine sequence, diastole. D: Cardiac magnetic resonance imaging, 4-chamber cine sequence, systole with evidence of apical ballooning. E: Cardiac magnetic resonance imaging, 2-chamber cine sequence, diastole. F: Cardiac magnetic resonance imaging, 2-chamber cine sequence, with evidence of apical ballooning in systole.

left ventricular function was evident on the echocardiogram.

The patient's evolution remained stable around the clinical cardiac symptomatology within the follow-up.

The admission electrocardiogram (EKG) for the patient showed notable ST-segment elevation in leads V2 to V6, along with negative T waves. These ECG findings are particularly significant in the context of Takotsubo Cardiomyopathy. Such patterns are emblematic of this condition, often mimicking acute myocardial infarction, yet occurring in the absence of coronary artery obstruction. The presence of these specific ECG changes in this patient aligns with the clinical diagnosis of Takotsubo Cardiomyopathy, highlighting the complex interplay of cardiac stressors and their manifestations on cardiac electrical activity in this unique syndrome (Fig. 1).

The comprehensive series of diagnostic images that were pivotal in evaluating the patient's cardiac condition. Panels A and B show the left and right coronary arteries respectively, both showing a Thrombolysis in Myocardial Infarction (TIMI) Flow Grade 3, indicating normal blood flow, which is atypical in the case of obstructive coronary events. Panels C through fare from cardiac magnetic resonance imaging (MRI), illustrating the diastolic and systolic phases in the 4-chamber and 2-chamber cine sequences. Notably, Panels D and F reveal the classic 'apical ballooning' observed in systole, a hallmark feature of Takotsubo Cardiomyopathy. These images collectively provide a clear visual representation of the cardiac anomalies consistent with Takotsubo Cardiomyopathy, supporting the diagnosis of Takotsubo Cardiomyopathy and ruling out obstructive coronary artery disease (Fig. 2).

2. Discussion

Chemotherapy remains a cornerstone in the treatment of various cancers. However, it's increasingly recognized that different types of chemotherapy can induce cardiovascular conditions, spanning a spectrum of structural diseases like heart failure and rhythm disorders [8]. Combinatorial chemotherapy regimens, tailored to specific types of cancer, are becoming more common. Literature review reveals several cases of TTS associated with such treatments. With the passage of time and the availability of different chemotherapies, their effects on the development of TSS have become evident. Various mechanisms have been proposed to explain this phenomenon. On one hand, they are based on a state of physical or psychological stress related to the chemotherapeutic treatment (Fig. 3) [10,11]. On the other hand, more specific explanations focus on the direct cardiotoxicity of the drug on the myocytes due to the appearance of free radicals, which affect the electrical activity and the conduction system of the heart [10,12]. The latter explanations are the most accepted for Carboplatin and Paclitaxel, both of which were administered to the patient.

Notably, TTS occurrences have been reported with Carboplatin combined with pemetrexed and pembrolizumab in 2020 [9], and with Carboplatin-Vinorelbine reported in 2019 [13]. In paclitaxel combinations, TTS was documented in 2011 with Paclitaxel, Hydroxyurea, 5-FU, and radiotherapy [10]. Interestingly, it was not associated with paclitaxel monotherapy until 2017 and later in 2021 [11], presenting clinical symptoms similar to our case. The EKG often shows an inverted T wave in these cases [12], suggesting that such combinations may increase the likelihood of these conditions, exacerbated by the malignancy load, itself an additional risk factor [14]. In this context, according to the InterTAK score, our patient reaches a score of 74 points with a probability of 92.9 % to the diagnosis of TTS, based on the gender (women), emotional stress, physical stress, the application of chemotherapy, and the EKG changes without ST depression, which shows a high diagnosis potential for the recent InterTAK score [15].

In this particular case, the TTS event occurred after the third chemotherapy cycle, in contrast to most events that typically occur after the first cycle [6]. Specifically, with the combined use of Carboplatin and Paclitaxel, only two cases in postmenopausal women have been reported in the literature, both in 2022 of records from the USA and Italy [16,17]. In both instances, the chemotherapy was combined with monoclonal antibodies: trastuzumab in a woman with breast cancer (grade 3 invasive ductal carcinoma) [18], and bevacizumab in a woman with peritoneal carcinomatosis from ovarian cancer [16]. In these cases, TTS manifested after several infusions of the monoclonal antibody alone (11 infusions of trastuzumab and 2 of bevacizumab, respectively), making our report the first to attribute TTS solely to Carboplatin and Paclitaxel chemotherapy. These patients, presenting symptoms varied

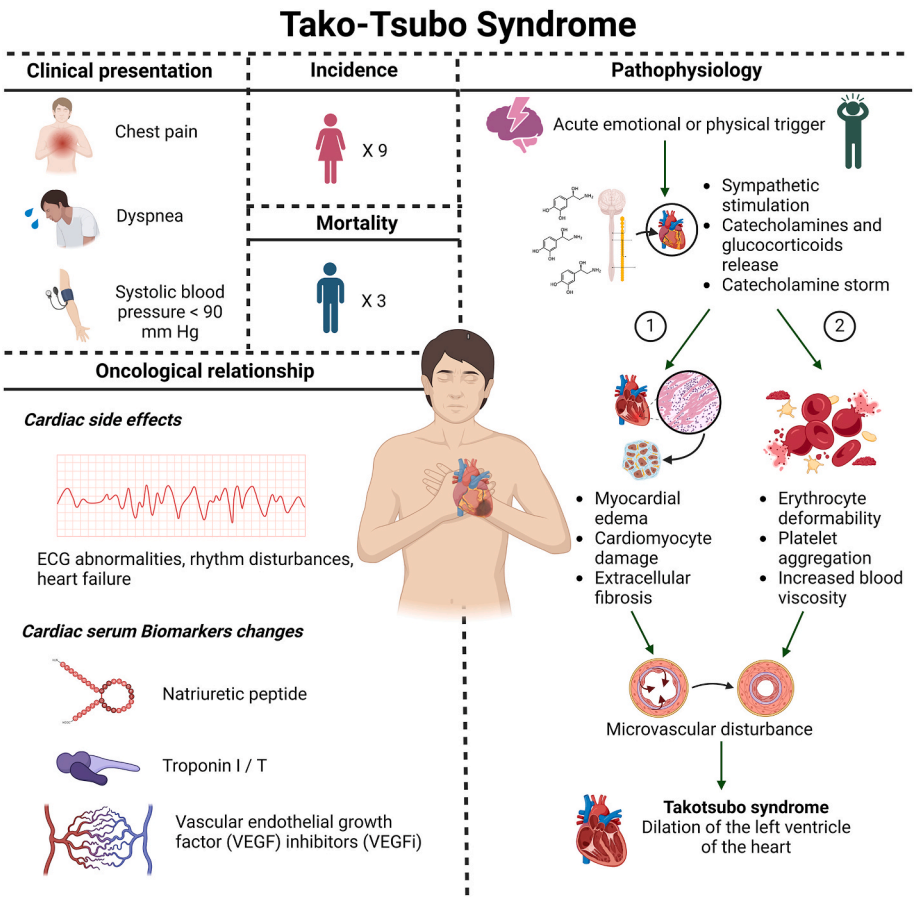

Fig. 3. Overview of the characteristics of Takotsubo syndrome. This infographic provides an overview of Takotsubo syndrome in the context of chemotherapy, highlighting its characteristics, association with cancer treatments, and the critical need for accurate diagnosis and management in oncological care.

significantly; one of the women was asymptomatic [16], while the other experienced intense chest pain, sweating, and nausea [18], mirroring our patient's pronounced symptoms. This underscores that the effect may not be immediate nor necessarily symptomatic. Given these variations, thorough follow-up and patient education on the potential effects of these chemotherapy combinations are crucial.

The most common demographic for TTS cases (>80 %) is postmenopausal women, with an average age of 69.5 years, similar to our patient's profile. Notably, our patient presented with a significant thromboembolic component, a rare comorbidity observed in only 1 % of cases [19]. Unlike the majority of TTS cases associated with breast cancer (26.2 %) and gastrointestinal system tumors (16.1 %) [15], our patient was diagnosed with cervical cancer.

Clinically and paraclinically, our patient met the acute phase criteria proposed by the Heart Failure Association of the European Society of Cardiology [7], she displayed anatomical characteristics such as transient abnormalities in left ventricular (LV) wall movement, evident in cardiac magnetic resonance imaging. The absence of atherosclerotic coronary artery disease, confirmed by coronary angiography, along with ECG changes showing ST segment elevation in five contiguous leads and T wave inversion, and a positive troponin biomarker, confirmed the diagnosis. Follow-up imaging showed reversal of myocardial dysfunction.

In patients with neoplasms, TTS has been linked to increased mortality and higher hospitalization costs due to morbidity [20]. Hence, its growing recognition is attributed to the increasing number of reported cases, underlining the importance of awareness and management of this disease in oncological care.

Thus, the current situation raises doubts regarding the optimal management of cancer patients who require chemotherapy and are exposed to a double risk mechanism for the development of TSS. In this context, given the presence of cardiac failure with reduced ejection fraction, the use of beta-blockers, angiotensin-converting enzyme inhibitors, or angiotensin II receptor blockers, and diuretics is recommended, when necessary, as was carried out in our patient [6]. Meanwhile, the approach to chemotherapy will be defined by discontinuing the administration of the trigger and waiting for the patient's recovery to resume treatment under close monitoring [21].

On the other hand, some authors have raised the possibility of finding specific treatments focused on mitigating the effects of chemotherapeutics on cardiac toxicity. In this sense, for the scenario that our patient experienced, pravastatin may appear as an option in the face of a possible activity that prevents oxidative stress on cardiac tissue [9]. Additionally, starting from one of the proposed routes, glucocorticoids and histamine receptor blockers have been suggested as prophylactic therapy for cardiotoxicity mediated by taxanes, including paclitaxel [8].

3. Conclusion

Takotsubo syndrome (TTS) remains a relatively rare clinical entity, particularly as an acute complication arising from chemotherapy. However, its incidence is gradually becoming more recognized in the context of combined chemotherapy regimens. Given the widespread use of these treatments in oncology, TTS should be a key differential diagnosis for symptoms mimicking acute myocardial infarction. This is crucial given the potential complications and implications TTS can have in patients undergoing cancer treatment. Recognizing and appropriately managing TTS in this setting is vital, as it not only impacts patient outcomes but also informs the careful monitoring and tailored approach required in the comprehensive care of oncological patients.

4. Consent statement

The authors have obtained the patient's written informed consent for dissemination and publication of the case report.

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CRediT authorship contribution statement

H.A. Nati-Castillo: Writing – original draft, Visualization, Software, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **David Aristizabal-Colorado:** Writing – original draft, Validation, Resources, Methodology, Investigation, Data curation, Conceptualization. **Carolina López Ordoñez:** Writing – original draft, Visualization, Validation, Supervision, Resources, Methodology, Investigation, Data curation, Conceptualization. **Diego Egas Proaño:** Writing – review & editing, Visualization, Validation, Supervision, Resources, Methodology, Investigation. **Esteban Ortiz-Prado:** Writing – review & editing, Validation, Supervision, Software, Methodology, Investigation, Formal analysis. **Juan S. Izquierdo-Condoy:** Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Project administration, Methodology, Investigation, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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