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A rare case of Takotsubo cardiomyopathy

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Abstract. – BACKGROUND: The recent advent of the cyclin-dependent kinase (CDK) 4/6 inhibitors has considerably evolved hormone receptor (HR)-positive/human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer treatment. Palbociclib, an orally administered pyridopyrimidine derivative, was the first CDK4/6 inhibitor to be introduced into daily clinical practice in combination with classic endocrine backbone, based on progression-free survival (PFS) benefit assessed in the pivotal PALOMA series of randomized clinical trials. Regarding its safety profile, neutropenia and leukopenia are the most common and well-defined adverse effects, while cardiac complications are rather scarce.

CASE REPORT: We present the rare case of a middle-aged female patient with HR+/HER2- metastatic breast cancer, without prior exposure to cardiotoxic antineoplastic agents, who developed Takotsubo cardiomyopathy (TTC) in the context of systemic therapy with palbociclib plus letrozole combination.

CONCLUSIONS: Pharmacovigilance and experimental studies are warranted to confirm any causative relationship and to explore the underlying pathophysiology, respectively.

Key Words:
Takotsubo cardiomyopathy, Heart failure, Palbociclib, Endocrine therapy, Breast cancer.

Background

Breast cancer represents a major health challenge worldwide, considering that it is the most commonly diagnosed malignancy and the second leading cause of cancer-related deaths among female[1]. Hormone receptor (HR)-positive/human epidermal growth factor receptor 2 (HER2)-negative molecular subtype remains the most prevalent diagnosis, accounting for approximately 75% of breast cancer cases[2]. The increased implementation of the novel endocrine targeted agents cyclin-dependent kinase (CDK) 4/6 inhibitors in hormone-sensitive breast cancer armamentarium has been correlated with survival benefit[3].

Indeed, the three commercially available, orally administered compounds ribociclib, abemaciclib, and palbociclib, combined with either fulvestrant or an aromatase inhibitor, have emerged as the current standard of care for the first-line treatment of HR+/HER2- metastatic breast cancer[4]. Noteworthy, CDK4/6 inhibition is not yet considered the preferred initial option for the visceral crisis, despite the reported 5-month overall survival (OS) improvement when compared to cytotoxic chemotherapy[5].

Palbociclib was approved in February 2015 by the Food and Drug Administration (FDA), in combination with the antiestrogen letrozole, for use in HR+/HER2- metastatic breast cancer in postmenopausal women, based on the phase 3 PALOMA-2 trial[6,7]. Although the primary endpoint of progression-free survival (PFS) was significantly prolonged, the secondary endpoint of OS did not meet statistical significance[8]. On the contrary, P-REALITY X real-world analysis demonstrated a 24% reduction in the risk of death among palbociclib plus aromatase inhibitor recipients *vs.* patients receiving aromatase inhibitors monotherapy (median OS of 49.1 *vs.* 43.2 months, respectively; HR: 0.76; 95% CI: 0.65-0.87; p-value<0.0001)[9].

In light of both prolonged and continuous usage of this regimen, it is crucial to promptly recognize and manage the short- and long-term treatment-related toxicities without compromising their therapeutic efficacy. Myelosuppression (neutropenia in particular), fatigue, and nausea are among the most frequent adverse events, while cardiotoxicity does not seem to represent a safety concern for this combo, at least at the recommended doses and schedule[6,7]. Herein, we report the uncommon case of Takotsubo syndrome during palbociclib/letrozole combinational treatment in a post-menopausal woman with HR+/HER2- metastatic breast cancer.

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Case Presentation

In this study, a 63-year-old, light-smoker, Caucasian female presented to the emergency department with oppressive chest pain and dyspnea at rest, both of acute onset. She did not report any symptoms indicative of a preceding viral syndrome affecting the gastrointestinal or respiratory tract.

Regarding her past medical history, the patient was diagnosed three and a half years prior to admission with HR+/HER2-invasive ductal carcinoma of her right breast, of initial stage IIIC, for which she opted solely for mastectomy. One-year post-surgery, upon disease recurrence with osseous metastases and pulmonary lymphangitic carcinomatosis, first-line chemotherapy with 3-week docetaxel was initiated, resulting in disease stabilization after the completion of six cycles. The combination of palbociclib plus letrozole was then commenced as first-line maintenance therapy, with acceptable toxicity, including grade 1 neutropenia, grade 2 nausea, and grade 1 alopecia, and partial response as best response within eight months.

Moreover, five months before her presentation, despite the absence of known pre-existing cardiovascular disease, our patient underwent 24-hour Holter monitoring due to transient episodes of palpitations and dizziness, which showed frequent (~32,000/24 hours) monomorphic premature ventricular contractions. Thus, 40 mg of oral propranolol once daily has been administered since then without any further investigation, providing symptomatic relief.

On physical examination upon admission, her body temperature was 36.6°C, her blood pressure was 110/65 mmHg with a heart rate of 68 bpm and an arterial oxygen saturation of 94% (FiO_2: 21%). Cardiac auscultation revealed the presence of S1, S2, without any murmurs, whereas lung auscultation revealed the presence of bibasal fine crackles. The rest of her clinical examination was unremarkable.

Pulmonary embolism was highly suspected due to her medical history. The differential diagnosis also included acute coronary syndrome (ACS), myocarditis, acute pericarditis, and malignant pleural effusion.

An electrocardiogram was performed, demonstrating normal sinus rhythm (Figure 1), while the laboratory analysis showed elevated troponin T values (62 ng/dl; normal <14 ng/dl), N-terminal pro-b-type natriuretic peptide (865 pg/ml; normal <125 pg/ml), and D-dimers (1,200 ng/ml; normal <500 ng/ml). A computed tomography pulmonary angiography excluded pulmonary embolism, pericardial or pleural effusion, and disease progression in the lungs, whereas the transthoracic echocardiogram in a four-chamber view mode was indicative of severe hypokinesis of the left ventricular (LV) mid segments, apical ballooning, left atrial enlargement, and reduced left ventricular ejection

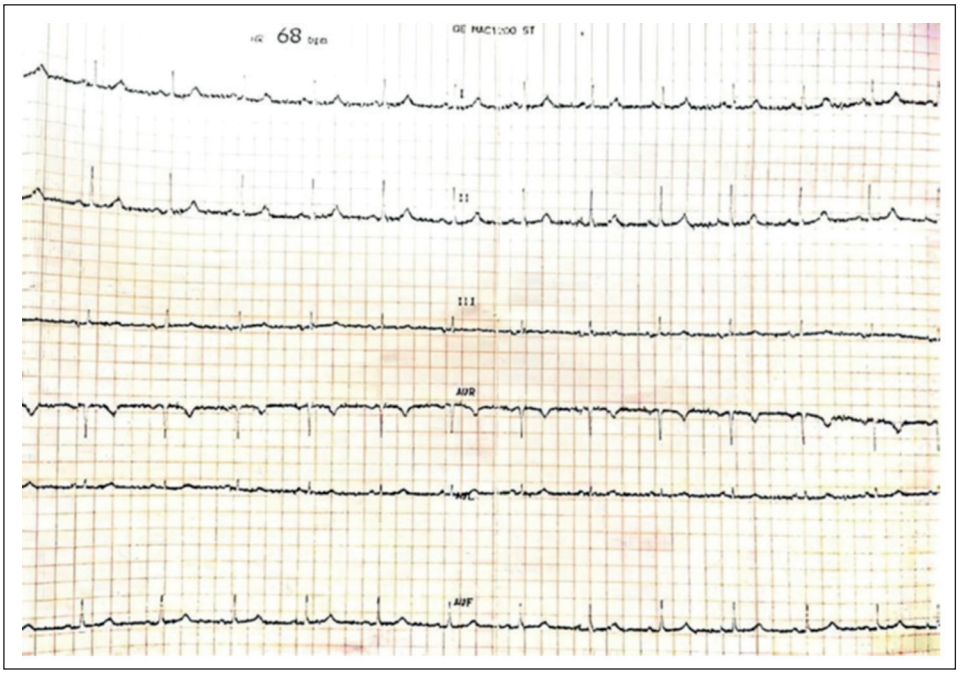

Figure 1. ECG recording at initial assessment.

fraction (LVEF: 40%; normal: 50% to 70%). The global longitudinal strain was also decreased (LV GLS: -11%; normal: -15.9% to -22.1%).

The subsequent coronary angiography was negative for both arterial occlusion and high-grade stenoses. The patient was admitted to the coronary care unit for continuous monitoring and optimal management.

Apart from withholding palbociclib/letrozole combo, the patient was initially treated as ACS accompanied by acute decompensated heart failure with triple antithrombotic therapy, a proton pump inhibitor to reduce gastrointestinal bleeding risk, an angiotensin-converting enzyme inhibitor, and the aldosterone antagonist eplerenone. After the exclusion of any culprit coronary artery disease (CAD), treatment was modified and included bisoprolol instead of propranolol, acetylsalicylic acid, ramipril, furosemide, eplerenone, low doses of atorvastatin, and esomeprazole. Upon spontaneous clinical improvement and normalization of cardiac enzymes, she was uneventfully discharged on day 7.

A cardiac magnetic resonance imaging (CMR) was performed two weeks later and revealed the absence of late gadolinium enhancement suggestive of fibrosis or necrosis, which is commonly seen in viral myocarditis[10], the presence of circumferential, transmural edema on mid-ventricular and apical images, with mild apical and LV anterior wall hypokinesia, resulting in an LVEF of 59% (Figure 2). Follow-up echocardiography, two months post-discharge, confirmed the complete resolution of LV systolic dysfunction (LVEF: 58%; GLS: -17.8%). Hence, a diagnosis of Takotsubo cardiomyopathy (TTC) was made.

With regards to her antineoplastic treatment, dose reduction was considered necessary for palbociclib (100 mg instead of 125 mg, day 1-21 of each 28-day cycle), whilst letrozole was re-initiated at the fixed dose of 2.5 mg/day, both as soon as the CMR displayed the reversibility of heart failure.

Discussion

TTC, first reported in 1990, is a rare, quite variegated syndrome characterized by acute and transient myocardial injury leading to LV systolic dysfunction in the absence of CAD[11]. It has been estimated that ~2% of patients, mainly women, presenting with troponin-positive, suspected ACS

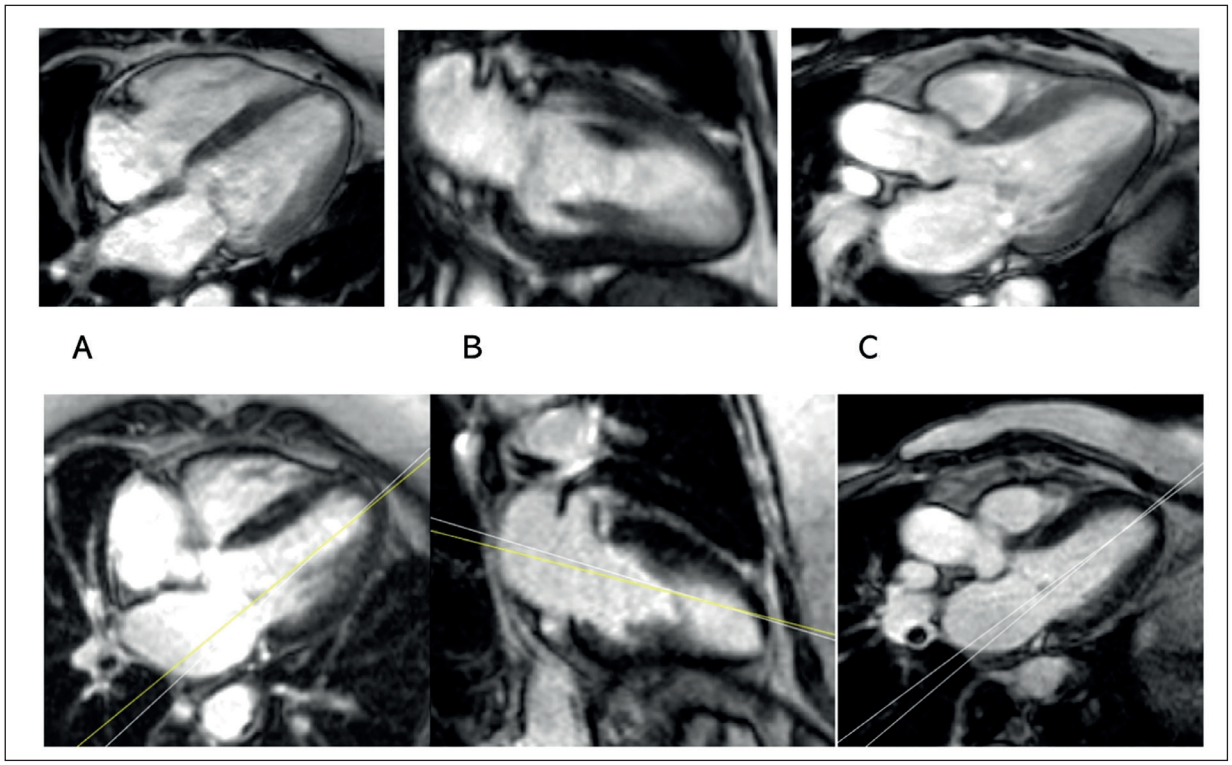

Figure 2. Cardiac magnetic resonance imaging two weeks post discharge showing the presence of diffuse, microscopic fibrosis and myocardial edema of the mid to apical LV. **A**, 4-chamber view; (**B**) 2-chamber view; (**C**) 3-chamber view.

(chest pain, and/or dyspnea, and/or syncope) will ultimately be diagnosed with TTC[11]. Currently, there are no universally accepted consensus criteria for its clinical diagnosis, but the Mayo Clinic diagnostic criteria[12] are among the most widely accepted. The underlying pathogenic mechanisms remain to be elucidated, yet physiological (i.e., respiratory failure, ischemic stroke, infection, drugs) and psychological (i.e., bereavement, anxiety, anger) triggers have been identified[11].

The association of TTC and cancer, most frequently breast cancer, has been suggested since 2008, predicting higher mortality risk both in the short- and long-term[13,14]. Besides emotional stress that arises with a cancer diagnosis, paraneoplastic syndrome and anticancer treatment-induced TTC cases have been reported[11,15]. In a meta-summary of 41 case reports, 36.5%, 9.7%, and 9.7% have been related to 5-fluorouracil, capecitabine, and trastuzumab, respectively[16]. Immune checkpoint inhibitors have also been linked with 17 cases of TTC syndrome, 88% of which have fully recovered[17]. Notably, in 5/10 (50%) cases, immunotherapy was re-introduced[17].

To the best of our knowledge, this is the first ever-known case of TTC in a breast cancer patient under novel endocrine therapy. Data from the pivotal PALOMA-2 trial demonstrated the scarcity of cardiovascular toxicity of palbociclib/letrozole combination; 0.9% of the 444 patients in the experimental arm experienced pulmonary embolism, whereas no cases of QTc prolongation, which has been linked with ribociclib had been reported[7]. A retrospective analysis of the US FDA Events Reporting System real-world database, on the contrary, showed that among the 69,821 palbociclib-induced adverse effects reported during the period January 2018 – September 2022, 3,765 (5.4%) and 1,466 (2.1%) were considered as vascular and cardiac, respectively[18]. Of note, seven events were attributed to "stress cardiomyopathy"[18].

Although a causative association between this endocrine-based regimen and the development of TTC cannot be unhesitatingly verified, decreased estrogen concentration has been associated with decreased vascular beta-2-adrenoceptor-mediated vascular response and reduced vasodilation[11].

Conclusions

Real-world pharmacovigilance studies will further explore the potential cardiac toxicity of this combinational endocrine therapeutic approach, whereas science research is eagerly awaited to explore and identify the underlying pathophysiological mechanisms. Last but not least, a multidisciplinary approach of breast cancer patients under novel targeted agents could improve diagnostic and therapeutic strategies for potential cardiovascular liabilities. Thus, collaboration within cardio-oncology is of utmost importance.

Authors' Contributions

O.F. and C.T. contributed to data collection, interpretation, literature searching, and manuscript drafting. N.K.S. and E.A.K. contributed to a critical review of the manuscript. All authors approved the final manuscript draft.

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Conflict of Interest

The authors have nothing to disclose that could influence the work reported in this article.

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Ethics Approval

Not applicable.

Informed Consent

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