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CASE REPORT

Neoadjuvant Chemotherapy: Friend or Foe

Cristian Nicolae POPA[a, b], Vladimir Dan BRATU[a, e], Elisa Cristina POPA[a, e], Daniela Elena DINU[a, b], Cristina IOSIF[c], Evelina CHIRITA[d], Ioan Nicolae MATES[a, b]

[a]"Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

[b]Department of General Surgery I, "Sf. Maria" Clinical Hospital, Bucharest, Romania

[c]Department of Pathology, "Sf. Maria" Clinical Hospital, Bucharest, Romania

[d]Department of Oncology, "Sf. Maria" Clinical Hospital, Bucharest, Romania

[e]Department of Cardiology and Cardiovascular Surgery, University Emergency Hospital, Bucharest, Romania

ABSTRACT

Introduction: *Most breast cancers require neoadjuvant chemotherapy and the response to primary systemic therapy (PST) is crucial for deciding on the surgical technique and predicting patient outcomes. However, chemotherapy also brings numerous side effects, with cardiovascular issues being some of the most significant, common and challenging to manage.*

Case presentation: *We present the case of a 71-year-old woman diagnosed with stage T2N1M0 Luminal B breast cancer. It was decided to initiate chemotherapy consisting of four cycles of FEC (5-fluorouracil 600 mg/m² on days 1 and 8, epirubicin 60 mg-90 mg/m² and cyclophosphamide 600 mg/m²), followed by four cycles of docetaxel (75 mg/m² every three weeks). Near the end of the treatment cycles, she developed new-onset angina with complex critical coronary lesions. This required assembling a multidisciplinary team to determine the optimal management strategy from cardiological, surgical, and oncological standpoints. Just when we thought we had found the optimal approach for managing ischemic heart disease, the situation became more complicated with the development of deep vein thrombosis, requiring a reassessment of the entire treatment plan.*

Conclusions: *Neoadjuvant chemotherapy is an important weapon against breast cancer but also a veritable enemy of cardiovascular diseases. The association of two major diseases requires a multidisciplinary team capable of making the best decisions to maximize benefits and minimize adverse effects.*

Keywords: breast cancer, neoadjuvant chemotherapy, atherosclerotic disease, deep vein thrombosis.

Address for correspondence:
Vladimir Dan Bratu
Department of Cardiology and Cardiovascular Surgery, University Emergency Hospital,
Splaiul Independentei, no. 169, Bucharest, Romania
Email: bratu.vladimir@gmail.com

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INTRODUCTION

Breast cancer is the most commonly diagnosed cancer in women worldwide and the leading cause of cancer-related mortality in global female population. According to the World Health Organization (WHO), in 2020 there were approximately 2.3 million new cases of breast cancer worldwide, representing 11.7% of all new cancer cases (1, 2).

Neoadjuvant chemotherapy plays a crucial role in the management of breast cancer, offering several potential benefits, including tumor downstaging, enabling breast-conserving surgery and providing early insights into the tumor's responsiveness to treatment, but may also have significant cardiovascular side effects (3-5). ❑

CASE REPORT

We describe the case of a 71-year-old female patient with menarche at the age of 12, currently in menopause for 14 years, non-smoker, grade I obesity – body mass index (BMI) 33 kg/m², grade 2 arterial hypertension – managed using an angiotensin-converting enzyme inhibitor (rampril 5 mg/day) and thiazide-like diuretic (indapamide 1.5 mg/day), without significant heredo-familial history, who came to "Sfanta Maria" Clinical Hospital, Surgery Clinic I, with a painless left breast tumor, in June 2022.

Clinically, a 4/3 cm formation is detected in the infero-external quadrant, with axillary lymph nodes measuring 2-3 cm. Laboratory findings showed mild anemia with hemoglobin 11.2 g/dL (13.0-17.0 g/dL), total cholesterol 213 mg/dL and LDL-c 112 mg/dL, with no other notable changes.

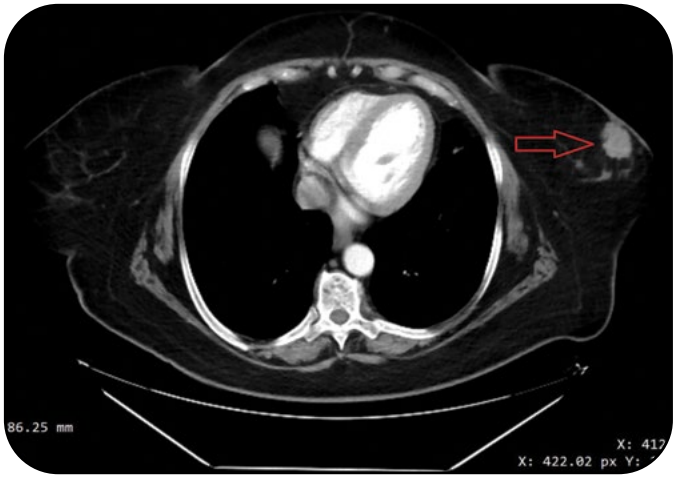

FIGURE 1. Chest computed tomography with contrast, arterial phase: pseudonodular tissue lesion in the infero-external quadrant of the left breast

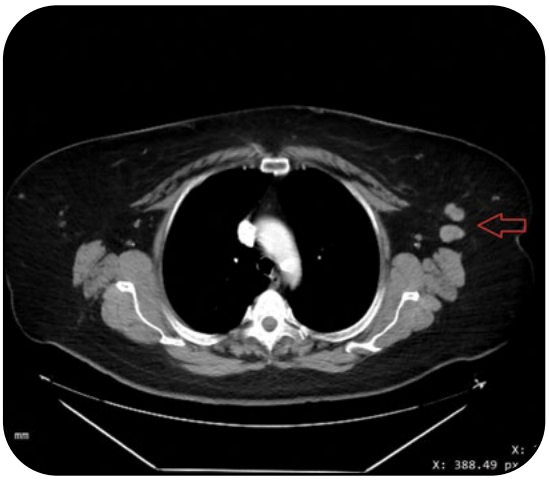

FIGURE 2. Chest computed tomography with contrast, arterial phase: left axillary lymphadenopathy

A chest computed tomography scan reveals a pseudonodular tissue lesion, iodophilic, with spiculated contours, measuring 33/23 mm, associated with mild diffuse thickening of the overlying skin and ipsilateral axillary lymphadenopathy, measuring up to 24/15 mm, most likely with a cancerous substrate. No secondary pulmonary or bone determinations were found.

For confirmation, a biopsy was performed using the TRU-CUT (6) method, which revealed tumor infiltration with histopathological features of invasive ductal carcinoma of no special type (NST), moderately differentiated (G2), with a histologic score of 7 (tubule formation = 3, nuclear pleomorphism = 2, mitotic count = 2); angio-lympho-neuroinvasion present; sclerohyaline stroma; minimal intratumoral lymphocytic infiltrate (TILs 1%); no ductal carcinoma *in situ* (DCIS) lesions detected. The immunohistochemical subtype is established as Luminal B: ER+100%, PR+100%, Ki67+50%, HER2 negative, stage T2N1M0 (distant metastases are excluded through comprehensive imaging evaluations) (7).

The patient was referred to the oncologist with indication for neoadjuvant chemotherapy. A schedule of four courses of both FEC (5-fluorouracil 600 mg/m² days 1 and 8 plus epirubicin 60 mg–90 mg/m² plus cyclophosphamide

600 mg/m^2) and Docetaxel (75 mg/m^2, every three weeks) treatment is established. Given the need to initiate anthracycline-based chemotherapy, a complete cardiac evaluation was performed. The patient was hemodynamically and respiratory stable, blood pressure (BP)=125/70 mm Hg in both upper limbs, heart rate (HR)=70 beats/minute, with no cardiovascular symptoms at the time of evaluation. Resting electrocardiogram (ECG) showed sinus rhythm, no pathological changes, and transthoracic echocardiography revealed a non-dilated left ventricle (LV) with preserved ejection fraction, mild concentric LV hypertrophy, without significant valve disease. In the context of newly diagnosed dyslipidemia, treatment with a statin (Rosuvastatin 40 mg/day) was initiated. Following her cardiac exam, neoadjuvant chemotherapy was initiated.

During primary systemic therapy (PST), the patient showed a favorable clinical response (reduction of tumor dimensions from 4 to 2 cm, left axilla without palpable lymph nodes), but towards the end of the PST, after the third cycle of docetaxel, she developed new onset typical angina and dyspnea on moderate exertion. Cardiology follow-up was performed, showing no significant changes in cardiac biomarkers CK-MB (creatine kinase-MB), hsTnI (high-sensitivity troponin I), NT-proBNP (N-terminal pro B-type natriuretic peptide) and no evolving changes in ECG or echocardiography. Given the presence of unstable angina in a patient with multiple cardiovascular risk factors, coronary angiography was planned and PST was stopped. Coronary angiography revealed an atheromatous plaque causing diffuse stenosis of approximately 80-90% in the mid-proximal segment of the left anterior descending artery (LAD), at the site of emergence of the first diagonal branch. No other significant coronary stenoses were observed.

Further management strategies were discussed, considering the patient's clinical condition, cardiovascular risk factors and ongoing cardiotoxic chemotherapy (8). A multidisciplinary team comprising an oncologist, surgeon, cardiologist and anesthesiologist was assembled to discuss various management options for this case. Although the lesion was a true bifurcation (Medina 0,1,1) lesion, and an upfront two stent technique, namely DK Crush (Double Kissing and Double Crush) (9) would generally be advisable, in this particular clinical setting it was considered inappropriate as it would require maintaining dual antiplatelet therapy (DAPT) for at least three months before surgery. Therefore, in order to prevent surgical delay, provisional stenting was the first choice in this case. Provisional

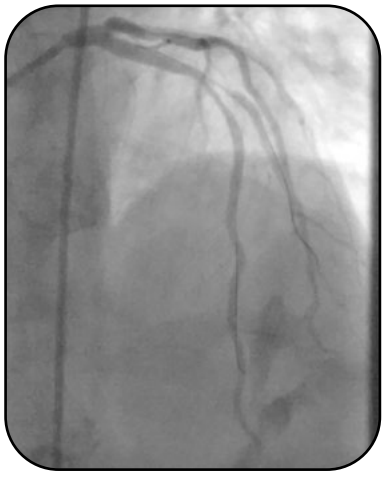

FIGURE 3. Coronary angiography: diffuse stenosis-80-90% in the mid-proximal segment of the left anterior descending artery (LAD) at the site of emergence of the first diagonal branch

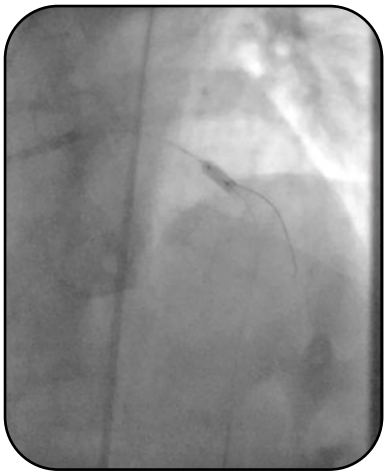

FIGURE 4. Coronary angiography: percutaneous coronary angioplasty (PCI) with pharmacologically active stent implantation at the mid-proximal segment of the left anterior descending artery (LAD)

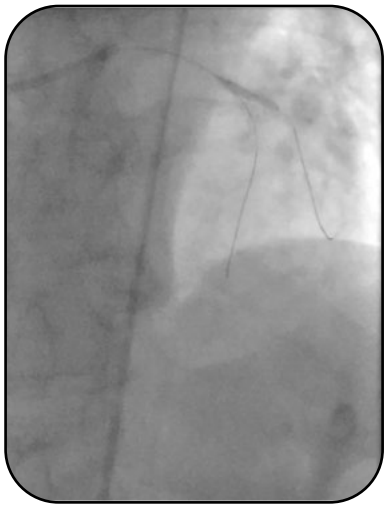

FIGURE 5. Coronary angiography: balloon dilation at the ostium of the first diagonal-residual stenosis of approximately 30%

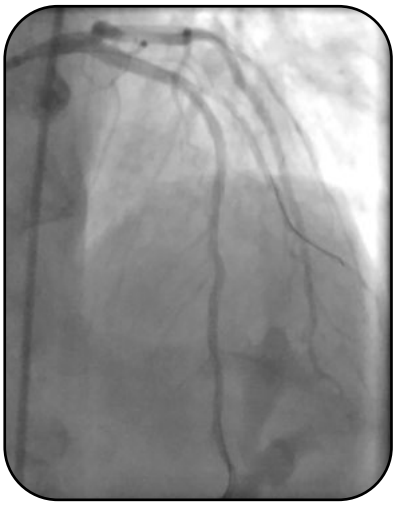

FIGURE 6. Coronary angiography: final angiographic results with TIMI flow

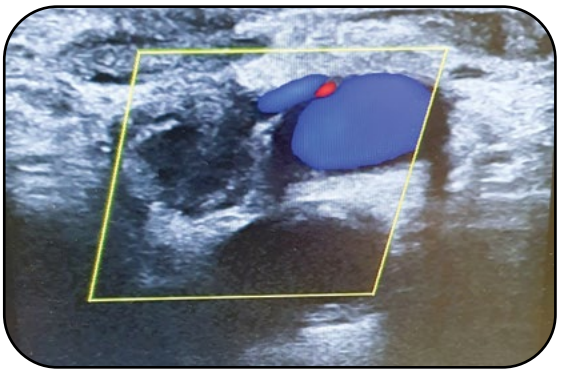

FIGURE 7. Vascular ultrasound: thrombus partially occupying the left common femoral vein

stenting of the LAD, followed by proximal optimization technique (POT), kissing balloon inflation (KBI) and re-POT was done with good result (30% residual stenosis of the ostium of the first diagonal), thus allowing early cessation of dual antiplatelet therapy in preparation for breast surgery.

In addition to the baseline treatment, DAPT with aspirin 75 mg daily and ticagrelor 90 mg twice daily for at least one year was introduced (PRECISE-DAPT score = 24). Ticagrelor would be discontinued three days before surgery, not earlier than one month, and resumed thereafter until one year.

Three days after leaving the hospital, the patient developed deep vein thrombosis in the left common femoral vein, extending to the mid-third of the deep femoral vein, which prompted a reassessment of the treatment plan. Oral anticoagulant (OAC) therapy (Apixaban 5 mg twice daily) was initiated after seven days of the low molecular weight heparin (LMWH) Enoxaparin 8000 UI twice daily. Due to the increased risk of bleeding, according to two major criteria (anticipated use of long-term OAC and active malignancy) and one minor criteria (Hb 11.2 g/dL) defined by the Academic Research Consortium for High Bleeding Risk (ARC-HBR), it was decided to initiate OAC without the initial seven days with Apixaban 10 mg twice daily and to stop aspirin one week after PCI. However, Ticagrelor was switched to Clopidogrel 75 mg daily, followed by discontinuation of aspirin and continued treatment with Clopidogrel and OAC for at least six months.

Considering the need for prompt surgical intervention, approximately one month after PCI, OAC was stopped 48 hours before the procedure. It was replaced by LMWH, with the last dose being administered 12 hours before surgery. However, perioperative monotherapy antiplatelet therapy (MAPT-aspirin) was maintained. The favorable response to neoadjuvant chemotherapy allowed for the selection of a conservative surgical intervention, involving left breast sectoral resection with axillary lymph node dissection. Postoperative recovery was favorable, with no significant bleeding. Histopathological examination of the biopsy specimen revealed a centrally located tumor formation measuring 2/0.8/2.2 cm: invasive breast carcinoma, NST, Grade 2, with a histologic score of 7 (tubule formation 3, nuclear pleomorphism 2, mitotic count 2); TILs approximately 10-15%; moderate desmoplastic reaction; absence of tumor necrosis; presence of vascular and perineural invasion; regressive changes noted in post-therapeutic context (fibrosis, hyalinization, granulomatous inflammation with focal foreign body giant cells). Peritumoral and distant tissue: breast tissue with foci of low nuclear grade intraductal carcinoma, architectural cribriform and papillary type, on a background of fibrocystic mastopathy. Resection margins free of malignancy, two out of 11 lymph nodes with carcinomatous metastasis (maximum tumor deposit size ~2 cm) – ypT2 N1a LVi (+) PNi (+) stage IIIA prognostic group AJCC, pPR (pathological partial response), RCB (residual cancer burden) score II.

Following the surgical intervention, the patient began adjuvant therapy with only immunotherapy (ER+ 100%, PR+ 100%). So far, she has responded to this treatment favorably, with no

recurrences. The positive response to chemotherapy (10, 11), the morphopathological and immunohistochemical characteristics of the neoplasm and the success of the surgical procedure all indicate a favorable 10-year prognosis (12).

From a cardiological perspective, the patient was initially monitored after one month, three and then six months (showing almost complete resolution of the deep vein thrombosis), remaining asymptomatic, gradually losing weight and maintaining strict control of other risk factors (LDLc 42 mg/dL with rosuvastatin 40 mg/day and ezetimibe 10 mg/day). After six months, it was decided to continue OAC at a prophylactic dose (Apixaban 2.5 mg daily) indefinitely or until the breast cancer is considered cured, along with Clopidogrel 75 mg daily until one year. ❑

DISCUSSION

Both breast cancer and cardiovascular diseases represent a global health issue with increasing incidence. Anthracyclines (Doxorubicin) and Taxanes (Docetaxel) are two commonly used chemotherapy agents in treating breast cancer. While effective in combating cancer, these drugs can have significant side effects on the cardiovascular system, contributing to the progression of atherosclerotic disease and increase the risk of thromboembolic events (5, 8).

Doxorubicin interacts with the DNA of cancer cells, inhibiting their replication and repair, but it is also well-known for its cardiotoxicity, which can worsen atherosclerosis through increased oxidative stress, inflammation and endothelial dysfunction. These processes can accelerate the formation and progression of atherosclerotic plaques. Docetaxel interferes with microtubule function during cell division, inhibiting mitosis and causing apoptosis in cancer cells. On the other hand, it can cause fluid retention and may increase the risk of thrombosis, which can further complicate an already atherosclerosis-prone environment. Both drugs can induce a systemic inflammatory response, which plays a crucial role in the progression of atherosclerosis. The production of reactive oxygen species (ROS) is increased in the presence of these chemotherapeutic agents, affecting the vascular wall and promoting atherogenesis. Chemotherapy can impair endothelial function, reducing nitric oxide production, thereby promoting vasoconstriction and platelet aggregation. In addition to the procoagulant status conferred by neoplasms, both docetaxel and doxorubicin are associated with an increased risk of deep vein thrombosis during or after administration (5, 13).

The particularity of our case consists of the onset of symptoms at the end of chemotherapy courses, without signs or symptoms contraindicating the continuation of PST until that moment, essentially providing the necessary time for chemotherapy to act favorably on breast cancer (RCB II, pPR, with an increasing TIL score from 1% at diagnosis to 10-15% after PST) (10, 11). On the other hand, the preexisting subclinical atherosclerotic disease has rapidly progressed under these two chemotherapy agents, leading to the development of critical coronary stenoses that posed a challenge for interventional resolution. The multidisciplinary team was compelled to balance two equally important concurrent conditions: symptomatic ischemic coronary disease with significant and complex coronary lesions requiring immediate revascularization, and breast cancer, which had responded favorably to PST and required surgical intervention as soon as possible. Given the complexity of the coronary lesions, the interventional technique of choice would have been angioplasty with stenting the bifurcation of the mid-proximal segment of the LAD, at the site of emergence of the first diagonal branch, preferably by deploying two stents at this level (DK Crush technique). Although this method involved complete revascularization with stents, it also carried a higher ischemic risk due to the inability to stop dual antiplatelet therapy earlier than three months, which would excessively delay the breast surgery. The chosen treatment option allowed for surgery to be performed within one month, with a minimal coronary cost – a residual stenosis of only 30% in the first diagonal branch after balloon angioplasty.

Moreover, the deep vein thrombosis occurring shortly after angioplasty imposed a reevaluation of antiplatelet and anticoagulant therapy. Due to the increased risk of bleeding, especially in the first month of anticoagulation after a thromboembolic event (active cancer, concomitant DAPT), it was decided to initiate anticoagulation directly with Apixaban 5 mg twice daily instead of the loading dose of 10 mg twice daily. It was decided to continue OAC for over

six months (at prophylactic dose), indefinitely, or until the completion of immunotherapy (considered to be the moment when cancer can be termed cured).

Despite all the associated pathologies and the difficulty in managing this case, it had a happy ending from all perspectives: surgical, oncological and cardiological. ❑

CONCLUSION

Cardiovascular diseases and cancer are two of the leading causes of mortality worldwide, and while they may seem unrelated, there are important connections between them. These share common risk factors, such as age, smoking, obesity, poor diet, lack of physical activity, and also overlapping pathophysiology, including inflammation, angiogenesis and oxidative stress (5, 13). Cancer treatment also has multiple adverse effects on the cardiovascular system making the management of these two conditions even more difficult.

Given the interplay between cardiovascular diseases and cancer, a multidisciplinary approach involving oncologists, surgeons, cardiologists and other specialists is essential for the comprehensive management of patients with both conditions. This approach ensures that potential cardiovascular risks associated with cancer treatment are identified and managed effectively, while also optimizing cancer treatment outcomes. ❑

Conflicts of interest: none declared.

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Informed consent: We obtained the patient's written signed consent for the publication of data for scientific purposes.

References

1. **Howlader N, Noone AM, Krapcho M, et al.** SEER Cancer Statistics Review, 1975-2016, National Cancer Institute. Bethesda, MD, based on November 2018.
2. **Bray F, Laversanne M, Sung H, et al.** Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2024;74:229-263.
3. **Spring M, Fell G, Arfe A, et al.** Pathologic Complete Response after Neoadjuvant Chemotherapy and Impact on Breast Cancer Recurrence and Survival: A Comprehensive Meta-analysis. *Clin Cancer Res* 2020;26:2838-2848.
4. **Sutton TL, Schlitt A, Stuart K, et al.** Time to surgery following neoadjuvant chemotherapy for breast cancer impacts residual cancer burden, recurrence, and survival. *J Surg Oncol* 2020;122:1761-1769.
5. **Papageorgiou C, Andrikopoulou A, Dimopoulos MA, Zagouri F.** Cardiovascular toxicity of breast cancer treatment: an update. *Review Cancer Chemother Pharmacol* 2021;88:15-24.
6. **Bdour M, Hourani S, Mefleh W, et al.** Comparison between fine needle aspiration cytology and tru-cut biopsy in the diagnosis of breast cancer. *J Surg Pak* 2008;13:19-21.
7. **Sinna H-P, Kreipeb H.** A Brief Overview of the WHO Classification of Breast Tumors, 4th Edition, Focusing on Issues and Updates from the 3rd Edition. *Breast Care* (Basel) 2013;8:149-154.
8. **European Society of Cardiology.** Guidelines on cardio-oncology. 26 Aug 2022.
9. **Allison Hall, Ivan Chavez, Santiago Garcia, et. al.** Double kissing crush bifurcation stenting: step-by-step troubleshooting. *EuroIntervention* 2021;17:e317-e325.
10. **Popa CN, Birla R, Mates IN, et al.** Breast cancer response to neoadjuvant chemotherapy quantified by residual cancer burden (RCB) score. *Farmacia* 2022;70:712-719.
11. **Popa CN, Birla R, Mates IN, et al.** Predictive Factors of Neoadjuvant Chemotherapy Response in Breast Cancer Validated by Three Anatomopathological Scores: Residual Cancer Burden, Chevallier System, and Tumor-Infiltrating Lymphocytes. *Cureus* 2024;16:e59391.
12. **Peto R, Davies C, Godwin J, et al.** Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100,000 women in 123 randomised trials. *Lancet* 2012;379:432-444.
13. **Yeh ETH, Tong AT, Lenihan DJ, et al.** Cardiovascular complications of cancer therapy: diagnosis, pathogenesis, and management. *Circulation* 2004;109:3122-3131.