A case of aplastic anemia associated with letrozole therapy in a patient with breast cancer
An oncological treatment challenge

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Abstract

Introduction: aplastic anemia is a rare hematological disorder characterized by bone marrow failure, resulting in pancytopenia with hypoplasia/aplasia due to the loss of hematopoietic stem cells. Approximately 70-80% of the cases are idiopathic, and the rest are mainly hereditary syndromes. An abnormal complete blood count generally arouses suspicion, and a bone marrow biopsy is required to confirm the diagnosis. This report presents the first case of aplastic anemia secondary to the use of letrozole.

Case presentation: We present the case of a 56-year-old female Venezuelan patient diagnosed with aplastic anemia during breast cancer treatment. After first- and second-line treatment, letrozole was administered as maintenance therapy. It was discontinued due to a suspected association with severe, persistent thrombocytopenia in the patient. A bone marrow biopsy confirmed the diagnosis of aplastic anemia. She was treated for both the breast cancer as well as the aplastic anemia, until she ultimately died due to breast cancer progression, seven years after being diagnosed with aplastic anemia.

Conclusions: Aplastic anemia is a rare hematological disorder, and its association with cancer treatment is often due to the toxicity caused by the different medications. This is a challenge for physicians in terms of selecting the proper treatment for oncological disease. This case presents a patient diagnosed with aplastic anemia during breast cancer treatment, emphasizing the importance of monitoring blood counts and recognizing possible complications associated with the use of chemotherapy. **(Acta Med Colomb 2024; 49. DOI: https://doi.org/10.36104/amc.2024.3148).**

Keywords: *aplastic anemia, letrozole, breast cancer, toxicity, hematological complications*.

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Introduction

Aplastic anemia is a rare bone marrow failure (BMF) blood disorder characterized by pancytopenia with hypoplasia/aplasia due to the loss of hematopoietic stem cells (HSCs) (1,2). The current literature describes four main mechanisms that cause this condition: 1) autoimmune mechanisms; 2) direct damage (medications, radiation, chemical products); clonal disorders; and 4) hereditary or non-hereditary genetic disorders (myelodysplastic syndrome, Fanconi anemia) and viral infections (Epstein Barr, hepatitis, HIV, herpes). However, approximately 70-80% of cases are idiopathic; the rest are mainly hereditary syndromes. The main signs and symptoms include bleeding due to thrombocytopenia, recurrent infections due to leukopenia, and fatigue and cardiorespiratory symptoms due to anemia. Along with the signs and symptoms, an abnormal complete blood count leads physicians to suspect this condition. Finally, a bone marrow biopsy confirms the diagnosis, showing an extremely hypocellular bone marrow with morphologically normal residual cells (2, 3).

It is uncommon in Western countries; the incidence in Europe is approximately 2-3 per million per year, and is two or three times greater in Asia. It has a biphasic distribution, with peaks at 10-25 years and over 60 years of age (2, 4). It is often associated with cancer treatment, due to the toxicity of the various drugs used in chemotherapy. There are multiple challenges in treating these cases due to chemotherapy-induced immunosuppression. Below, we present the clinical case of a patient diagnosed with aplastic anemia while being treated for breast cancer.

Case presentation

This was a 56-year-old Venezuelan patient who had lived in Bogotá since 2019. She had no significant family history,

a G0P0 gynecological history and O+ blood. Her personal medical history included the use of vaginal estrogens and medroxyprogesterone since 2002, following unilateral oophorectomy due to endometriosis. She had no history of alcohol consumption or smoking.

In December 2008, the patient consulted with a complaint of a mass in her right breast and was diagnosed with invasive lobular carcinoma. In January 2010, she underwent a quadrantectomy and axillary resection, with 11 tumor-involved lymph nodes. From February to October of that year, she received adjuvant therapy in Venezuela, including six cycles of chemotherapy using the AC (Adriamycin/cyclophosphamide) regimen, followed by 12 weeks of weekly paclitaxel. After this, she received radiation as consolidation treatment and tamoxifen as an adjuvant hormone therapy until 2012. During follow-up, a new mass was found in the right breast in December 2012, with a biopsy confirming local recurrence. Therefore, she underwent bilateral mastectomy, with a pathology report that indicated HER2 overexpression negativity, 60% estrogen receptor positivity, 5% progesterone receptor positivity and a Ki-67 index of 80%. Extracapsular tumor involvement was also found in an ipsilateral axillary lymph node.

From February to May 2013, she received six cycles of adjuvant therapy with gemcitabine and carboplatin. Then she was given letrozole as adjuvant hormone therapy, which was discontinued in November 2013 due to severe, persistent thrombocytopenia. She was seen by hematology, diagnosed with aplastic anemia, and given antithymocyte globulin (ATG) treatment followed by cyclosporine for two years up to April 2018, with moderate residual thrombocytopenia. At the same time, the patient moved to Colombia, and her oncologist replaced her hormone therapy with fulvestrant, beginning in October 2015. She subsequently developed slow bone progression in February 2019 and a new axillary skin recurrence in April 2020, and therefore her treatment was changed to exemestane plus palbociclib, although the latter was not tolerated due to severe thrombocytopenia and neutropenia. A new enlarged left axillary lymph node was biopsied and showed triple negative breast carcinoma, and

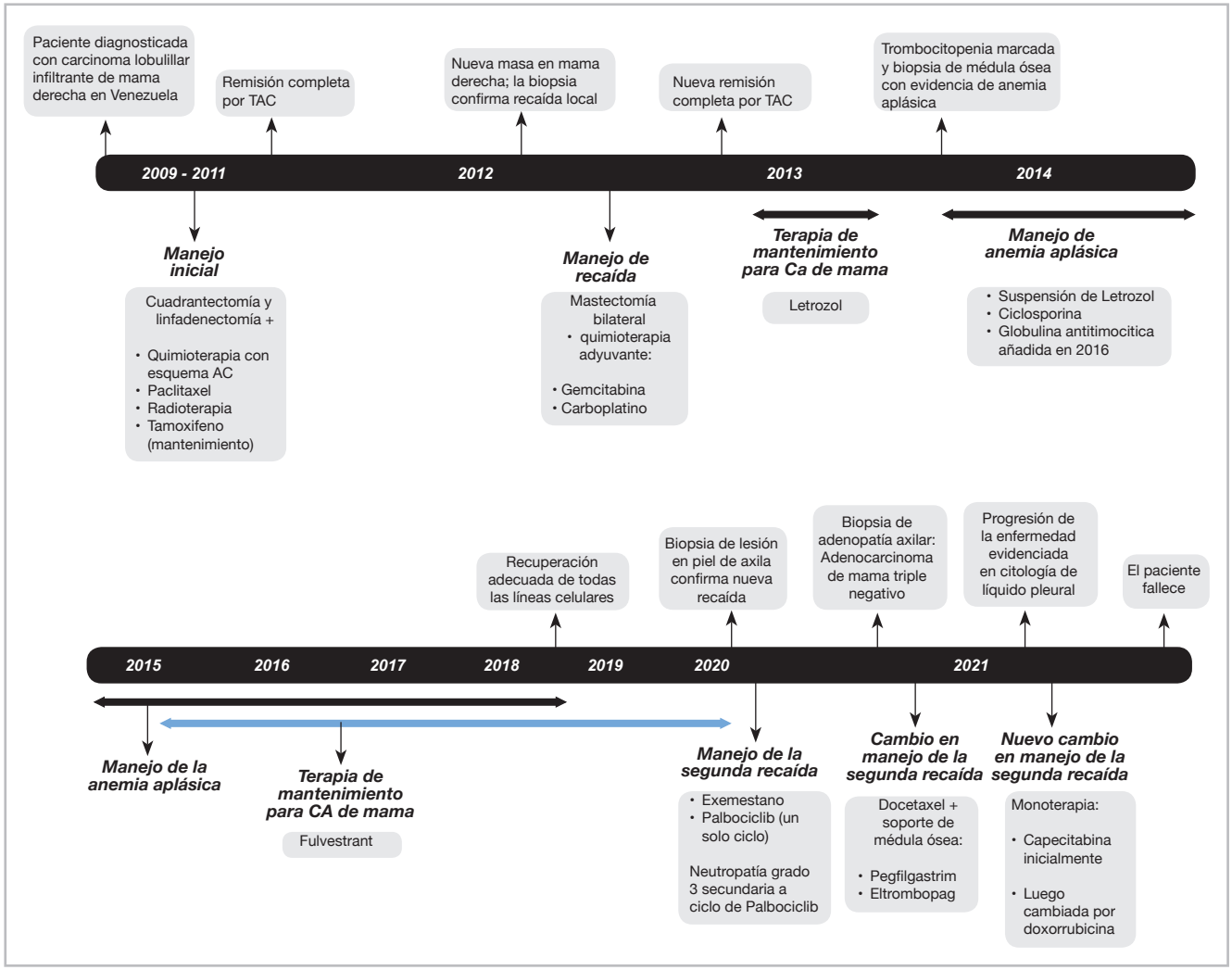

Figure 1. *Timeline showing the patient's clinical course from diagnosis to death. Source: Authors' files.*

biweekly docetaxel treatment was started in October 2020, adjusted for aplastic anemia. Hematology ordered supportive pegfilgrastim and eltrombopag, and she received this chemotherapy regimen beginning on November 12, 2020, with new local-regional and pleural progression confirmed by pleural fluid cytology in May 2021. In light of this, she began treatment with an adjusted dose of capecitabine from June 2021 to September 2021, with new progression, for which she was started on liposomal doxorubicin. Finally, in November 2021, the patient died due to rapid tumor progression. The timeline and progression of the case is presented in Figure 1.

Discussion

Hormone therapy for postmenopausal patients with hormone receptor-positive breast cancer has significantly improved their survival. Letrozole is a third-generation aromatase inhibitor that is a non-steroidal triazole derivative. It is currently one of the most potent inhibitors with the best tolerability profile. The most common side effects of aromatase inhibitors, according to a systematic review and meta-analysis of more than 24,000 postmenopausal breast cancer patients, are a higher risk of hot flashes (39.3%), arthralgias (28.9%) and vaginal dryness (26.1%) (5). Hematological toxicity is uncommon. One case of pancytopenia caused by letrozole treatment was reported in 2002, and the patient recovered her cell counts after discontinuing the medication (6). As far as we know, this is the first reported case of a patient developing letrozole-associated aplastic anemia.

Since many of the drugs used to treat breast cancer have hematologic toxicity, aplastic anemia in a patient who needs cytotoxic chemotherapy, which also causes myelosuppression, poses a treatment challenge. Oncologists should consider adjusting the chemotherapy dose and administration regimen, keeping in mind that some drugs cannot be administered at all. This clinical case required the joint intervention of hematology and oncology to achieve the best possible control of the patient's condition. The diagnosis of letrozole-associated aplastic anemia was made by ruling out other causes, due to the patient's clinical setting, and was confirmed through a bone marrow biopsy. The patient initially responded adequately to early treatment with ATG and cyclosporine and had acceptable cell counts for several years.

It is also important to note that, given the wide range of possible diagnoses (including the need to rule out myelophthisis), pancytopenia in patients with cancer must be studied with a bone marrow biopsy. Pancytopenia due to bone marrow infiltration from breast cancer has also been reported in these patients, and therefore the definitive diagnosis is always based on the histological analysis, which was crucial in our case to guide the strategy and continuance of subsequent cancer treatment.

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