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Case Report

Unusual Presentation of Secondary Chronic Myeloid Leukemia in a Metastatic Breast Cancer Patient Receiving Cyclin-dependent Kinase 4/6 Inhibitor Therapy: A Case Report

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Abstract

An association between breast cancer treatment and secondary chronic myeloid leukemia (CML) has rarely been reported. In this report, we present a 62-year-old postmenopausal woman initially diagnosed with hormone receptor (HR)-positive, HER2-negative metastatic breast cancer who subsequently developed CML with an atypical presentation. The patient was initially diagnosed with Stage IV invasive ductal carcinoma. Treatment included modified radical mastectomy, palliative radiotherapy, chemotherapy, followed by endocrine therapy and the cyclin-dependent kinase 4/6 (CDK4/6) inhibitor, palbociclib. Six years after the breast cancer diagnosis, regular blood tests revealed thrombocytosis and basophilia. Even though bone marrow studies only revealed megakaryocytic proliferation, chromosomal analysis and genetic testing confirmed the diagnosis of chronic phase CML. This case not only demonstrates the occurrence of CML with an atypical presentation under CDK4/6 inhibitor treatment but also further indicates that patients receiving long-term CDK4/6 inhibitor therapy may develop secondary malignancies. In addition, while radiotherapy and chemotherapy are established risk factors for therapy-related myeloid neoplasms, the association between CDK4/6 inhibitors and secondary CML development, as well as their influence on the clinical outcomes of CML, remains poorly understood. Regarding management, data on the concurrent administration of BCR-ABL1 tyrosine kinase inhibitors and CDK4/6 inhibitors are limited. With CDK4/6 inhibitors becoming standard treatment for metastatic HR-positive breast cancer, longer follow-up and further studies are needed to clarify their relationship with secondary CML and to optimize treatment for these patients.

Keywords: Case report, chronic myeloid leukemia, cyclin-dependent kinase 4/6 inhibitors, metastatic breast cancer, tyrosine kinase inhibitor

Introduction

Breast cancer has been the leading cause of cancer morbidity and mortality among women worldwide for decades.

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Standard treatment for breast cancer encompasses multiple modalities tailored to specific subtypes. The occurrence of secondary hematologic malignancies, especially acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS), has been well described in breast cancer survivors, partly due to chemotherapy with anthracycline and/or radiotherapy during the course of treatment.[1] However, secondary chronic myeloid leukemia (CML) after breast cancer treatment has rarely been reported, and no previous study has reported the development of CML in patients undergoing cyclin-dependent kinase 4/6 (CDK4/6) inhibitor treatment. Here, we report a valuable case of postmenopausal woman diagnosed with hormone receptor (HR)-positive metastatic breast cancer (MBC) who developed secondary CML with an atypical presentation after receiving palliative radiotherapy, chemotherapy, endocrine therapy, and a CDK4/6 inhibitor.

Case Report

The patient was a 62-year-old female with leiomyomata uteri posttotal abdominal hysterectomy in September 2014. She presented to our orthopedic clinic in June 2017 with left upper extremity tenderness and decreased range of motion for months. A radiographic evaluation showed an osteolytic lesion with pathologic fracture in the left humerus, and a physical examination revealed a palpable right breast mass at the 12 o'clock position, 2 cm from the areolar margin. Ultrasound-guided core needle biopsy confirmed invasive ductal carcinoma. Immunohistochemical analysis demonstrated strong estrogen receptor positivity (90%), progesterone receptor positivity (90%), HER2/neu negativity (score 0), and a Ki-67 index of 25%. Staging workup with contrast-enhanced computed tomography and whole-body technetium-99 m bone scintigraphy confirmed oligometastasis of the bone. She was classified as having postmenopausal status due to amenorrhea for more than 1 year at diagnosis.

The patient underwent wide excision of the left humeral metastasis with open reduction and internal fixation, along with modified radical mastectomy with level I-II axillary lymph node dissection. A histopathological examination confirmed invasive mammary carcinoma with osseous metastasis, staged as pT3N1M1, Stage IV according to the 7th edition of the American Joint Committee on Cancer. She received palliative systemic chemotherapy with docetaxel and cisplatin for 4 cycles between August and October 2017, along with radiotherapy to the left humeral metastasis (3000 cGy/10 fractions). Subsequently, she received letrozole with palbociclib on a 3-weeks-on/1-week-off schedule. Denosumab monthly was added to manage the bone metastasis. Regular follow-up with computed tomography has shown no disease progression to date.

Six years after the breast cancer diagnosis, hematological investigations revealed isolated thrombocytosis with basophilia in September 2023. A physical examination and imaging showed no splenomegaly or breast cancer progression. Molecular genetic analysis for *JAK2*V617F, *Jak2*Exon12, *CALR*, and *MPL* mutations was negative. Serial blood counts demonstrated progressive leukocytosis and persistent thrombocytosis. She finally agreed to undergo diagnostic bone marrow studies in July 2024, which showed a high myeloid/erythroid ratio and increased megakaryocytes, consistent with myeloproliferative neoplasm [Figure 1]. Chromosome analysis revealed Philadelphia chromosome, and BCR-ABL1 fusion transcript analysis confirmed e14a2 (b3a2) BCR: ABL1/t(9;22) fusion variant. Chronic phase CML was diagnosed, with a Sokal risk score of 5.2 (high-risk). Tyrosine kinase inhibitor (TKI) therapy with imatinib mesylate was initiated at 200 mg daily in August 2024 without adjusting palbociclib. A complete hematologic response was achieved in November 2024, but only a major cytogenetic response (MCR) in December 2024. Imatinib was escalated to 300 mg daily in December 2024. She remained in MCR despite dose escalation until March 2025, prompting a switch to nilotinib in April 2025 [Figure 2].

Discussion

The patient in this case had HR-positive, HER2-negative-MBC with oligometastases to the bone. She received multimodal treatment initially, followed by endocrine therapy with a CDK4/6 inhibitor. Isolated thrombocytosis was detected incidentally 6 years after the diagnosis of breast cancer, and CML was finally diagnosed. We present this case to highlight the atypical initial manifestation of CML, concerns about synergistic hematological toxicities associated with concurrent BCR-ABL 1 TKI and CDK4/6 inhibitor treatment, and the potential risk of CML development under CDK4/6 inhibitor treatment.

Cyclin-dependent kinase 4/6 inhibitors may result in atypical presentations of chronic myeloid leukemia

CML is a clonal hematopoietic stem cell disorder due to t(9;22)(q34; q11) translocation, leading to abnormal BCR:: ABL fusion gene rearrangements. CML typically presents as leukocytosis with elevated immature granulocytes, basophilia, and eosinophilia in the peripheral blood. Mild anemia and thrombocytosis are commonly seen.[2] Rarely, CML may present with atypical features such as isolated thrombocytosis without

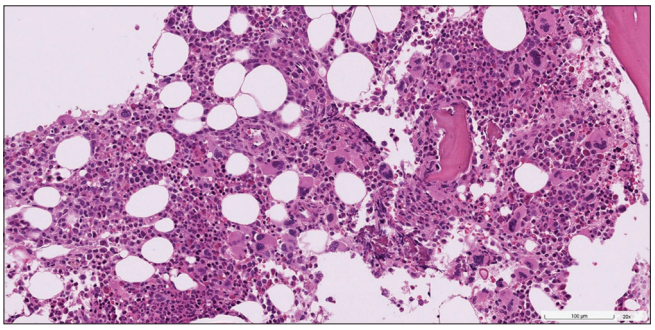

Figure 1: Bone marrow trephine biopsy. A bone marrow biopsy showed hypercellularity with myeloid hyperplasia and proliferated hyposegmented megakaryocytes. (Scale bars 100 mm, ×20)

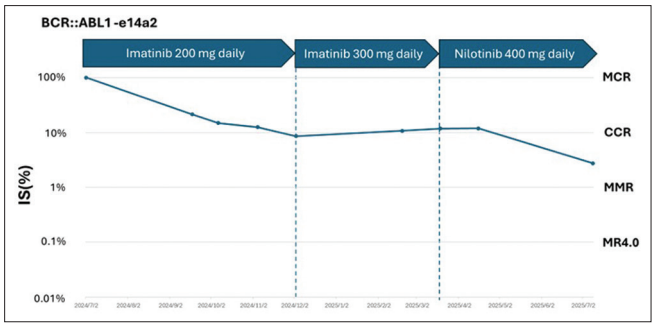

Figure 2: Molecular response of BCR:: ABL1 transcript. Imatinib 200 mg daily was initiated in August 2024. Major cytogenetic response (MCR) was achieved in December 2024. The dose was titrated to 300 mg daily. The patient remained in MCR in March 2025 despite dose escalation. Because a major molecular response was not achieved, imatinib was shifted to nilotinib in April 2025. IS: International scale, MCR: Major cytogenetic response, CCR: Complete cytogenetic response, MMR: Major molecular response, MR4.0: Molecular response 4.0

leukocytosis, leading to delayed diagnosis or misdiagnosis as essential thrombocythemia.[3] Our case had a similar atypical presentation, with asymptomatic thrombocytosis and basophilia without splenomegaly. Leukocytosis developed after a few months while under palbociclib treatment. Palbociclib commonly causes hematologic adverse events, especially neutropenia. In the phase 3 PALOMA-2 trial, 79.5% of the patients in the palbociclib-letrozole arm experienced neutropenia of any grade, with 66.5% having Grade 3 or higher.[4] In addition, thrombocytopenia occurred in 15.5% of the patients at any grade and in 1.6% above grade 3.[4] This suggests that palbociclib may mask the characteristic CML leukocytosis, resulting in atypical presentations such as isolated thrombocytosis due to the hematological effects of palbociclib.

Chronic myeloid leukemia secondary to other malignancies

Ionizing radiation exposure is the most well-characterized risk factor for developing CML, as it was the most common leukemia among survivors of the atomic bombings of Hiroshima and Nagasaki during World War II.[5] Numerous studies have reported myeloid neoplasms secondary to chemotherapy and/or radiation therapy,[6] as well as secondary malignancies in CML patients. However, CML secondary to other malignancies has been less studied.[7] Among therapy-related leukemia, therapy-related CML only accounts for 1.2%–13.3% of cases.[8,9] Several retrospective studies reported that secondary CML accounted for 3.6%–13% of newly diagnosed CML cases.[7,10-12] The median time from diagnosis of the primary neoplasia to the diagnosis of CML has been reported to range from 65 to 99 months.[7,10,12]

An Italian retrospective study of 617 patients with newly diagnosed CML, including 48 with previous malignancies, found that cytogenetic and molecular responses to TKIs among secondary CML patients were similar to those with standard CML.[7] The median times to complete cytogenetic response and major molecular response in those with secondary CML were 3 and 9 months, respectively, and the median overall survival from diagnosis was 53 months,[7] shorter than in *de novo* CML (10-year survival rate of 80%–90% in the TKI era). While secondary CML has a similar responsiveness to TKIs, it is associated with inferior overall survival, potentially due to the unfavorable prognosis of underlying primary malignancies. Despite the less favorable outcomes in secondary CML, current clinical guidelines do not recommend differential therapeutic approaches due to the limited number of cases for comprehensive analysis.

The clinical course in our case is consistent with previous studies, with a latency of 73 months before CML diagnosis. However, our case had a poorer response to TKI therapy, achieving only MCR after 5 months of imatinib treatment.

Secondary chronic myeloid leukemia after breast cancer treatment

Secondary leukemias developing after breast cancer treatment, including chemotherapy and radiotherapy, are mostly AML and MDS. Radiation and chemotherapy may have a synergistic effect in the development of secondary AML/MDS.[1] Of the available chemotherapies, mitoxantrone and anthracyclines are significantly associated with an increased risk of AML/MDS compared with cyclophosphamide.[13] The anthracyclines-AML/MDS association is especially important for breast cancer, as anthracyclines are standard treatment.[14] Unlike secondary AML/MDS, secondary CML after breast cancer has only been described in a few case reports.[15,16] In a population-based study from the Surveillance, Epidemiology, and End Results database of 474,866 females with breast cancer, 178 were later diagnosed with CML. In addition, the risk of CML increased significantly after the diagnosis of breast cancer, particularly within the first 5 years.[17] Radiotherapy, chemotherapy, and positive HR were associated with a significant increase in CML risk.[17] The median overall survival of CML after breast cancer was 28 months,[17] shorter than that of secondary CML reported in the previously mentioned studies.

Possible etiologies of chronic myeloid leukemia in our case

Frequently reported etiologies of secondary CML include genetic predisposition, prior chemotherapy and radiotherapy, although the contributions of these factors are still under debate.[18] Our case received multimodality treatment including radiotherapy, chemotherapy, long-term aromatase inhibitor (AI) treatment, and a CDK4/6 inhibitor. AI has been an important component of standard treatment for HR-positive breast cancer for decades. A meta-analysis of extended AI treatment in patients with early HR-positive breast cancer revealed that AI treatment did not significantly increase the risk of developing secondary malignancies.[19] Since 2016, CDK4/6 inhibitors have been the standard treatment for advanced HR-positive breast cancer due to the success of the phase 3 PALOMA-2 trial.[4] To date, no association between secondary malignancies and CDK4/6 inhibitors has been reported. However, adverse events regarding CDK4/6 inhibitors need

longer follow-up. Although preclinical studies have shown significant efficacy against acute leukemia,[20] the association between CDK4/6 inhibitors and the development of secondary CML remains poorly understood.

Concomitant use of BCR-ABL 1 TKIs and cyclin-dependent kinase 4/6 inhibitors

This is the first documented case report to describe the concurrent administration of imatinib and palbociclib. We initiated imatinib at a reduced dosage while maintaining the standard palbociclib regimen, given the anticipated risk of synergistic hematological toxicities associated with CDK4/6 inhibition. Before the diagnosis of CML, prolonged palbociclib monotherapy at a standard dosing schedule resulted in mild hematological adverse effects, manifesting as Grade 1 leukopenia and neutropenia. The patient initiated imatinib treatment in August 2024 and subsequently developed Grade 2 leukopenia and Grade 3 neutropenia in the 1st month of treatment, consistent with additive hematological toxicity. Due to the suboptimal therapeutic response, imatinib was escalated to 300 mg daily. While no exacerbation of the hematological toxicities was observed, there was also no increase in therapeutic efficacy. Given the persistent inadequate response, treatment was shifted from imatinib to nilotinib 400 mg daily, which demonstrated a more favorable hematological safety profile than imatinib.[21]

Currently, no clinical guidelines recommend dose adjustment strategies for the concurrent administration of BCR-ABL 1 TKIs and CDK4/6 inhibitors. From a pharmacokinetic perspective, imatinib, nilotinib, and palbociclib are predominantly metabolized via the cytochrome P450 (CYP) 3A4 pathway. Both imatinib and nilotinib function as moderate competitive CYP3A4 inhibitors,[22,23] whereas palbociclib has weak CYP3A4 inhibitory activity.[24] The first workshop on pharmacology and management of CDK4/6 inhibitors, organized by the Spanish Breast Cancer Cooperative Group SOLTI, established consensus recommendations to avoid combining palbociclib with potent CYP3A inhibitors. When such combinations are unavoidable, dose reduction of palbociclib to 75 mg is recommended. For combinations involving moderate CYP3A4 inhibitors, such as imatinib and nilotinib, the dose of palbociclib can be increased. Closely monitoring toxicities without dose modification is advised.[24] Furthermore, the risk of drug interactions between imatinib/nilotinib and palbociclib is classified as Risk Category C in UpToDate Lexidrug, warranting vigilant monitoring for toxicities. Given the limited clinical data regarding the concomitant use of imatinib/nilotinib and palbociclib, the combination of imatinib or nilotinib with palbociclib without dose reduction, accompanied by rigorous monitoring, is a reasonable therapeutic strategy based on current clinical evidence.

In summary, we report a patient with HR-positive MBC who developed secondary CML with the atypical presentation of isolated thrombocytosis 6 years after the diagnosis of breast cancer. This case highlights the potential risk of developing secondary CML among breast cancer patients. In addition to prior radiotherapy and chemotherapy, our patient also received CDK4/6 inhibitors, which may mask the characteristic leukocytosis, resulting in an atypical presentation. Further studies are needed to clarify the association between CDK4/6 inhibitors and secondary malignancies. Regarding management, the concurrent administration of imatinib/nilotinib and palbociclib appears to demonstrate synergistic hematological toxicities. Concomitant therapy with imatinib/nilotinib and palbociclib at standard dosing, accompanied by close hematological monitoring, may be a reasonable initial therapeutic approach.

Declaration of patient consent

This study was performed in accordance with and conforming to the Declaration of Helsinki. The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

Author contributions

Concept: Yi-Yang Chen; Design: Chia-Hung Wu, Yi-Yang Chen; Definition of intellectual content: Chia-Hung Wu, Yi-Yang Chen; Literature search: Chia-Hung Wu, Wen-Yung Tsai; Clinical studies: Chia-Hung Wu, Wen-Yung Tsai; Experimental studies: Jing-Lan Liu; Data acquisition: Chia-Hung Wu, Wen-Yung Tsai; Data analysis: Chia-Hung Wu; Statistical analysis: Chia-Hung Wu; Manuscript preparation: Chia-Hung Wu; Manuscript editing: Chia-Hung Wu; Manuscript review: Yi-Yang Chen. All authors have read and agreed to the final version of the manuscript.

Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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