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Oncology

A RARE CASE OF CHRONIC MYELOID LEUKEMIA AFTER BREAST CANCER

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ABSTRACT Therapy-related myeloid neoplasms (t-MN) are known late complications after treatment of primary malignancy. Secondary malignancies are clinically important phenomena following treatment with chemotherapy. Lifetime risk of t-MN is estimated to be 1 to 5%. T-TMNs typically include acute myeloid leukemia, myelodysplastic syndrome, and myeloproliferative neoplasms. Their occurrence has been thoroughly documented and studied. Development of chronic myeloid leukemia (CML) subsequent to treatment is a considerably rarer event, such that it remains infrequently reported in the literature. Complicating this, population and cytogenetic characteristics of primary and secondary CML appear largely homogenous, making it uncertain if reported cases represent true secondary malignancies or are rather due to de novo mutations. CML has rarely been reported following treatment of breast cancer. A case of CML that developed in the patient who was treated for carcinoma breast seven years earlier, is reported.

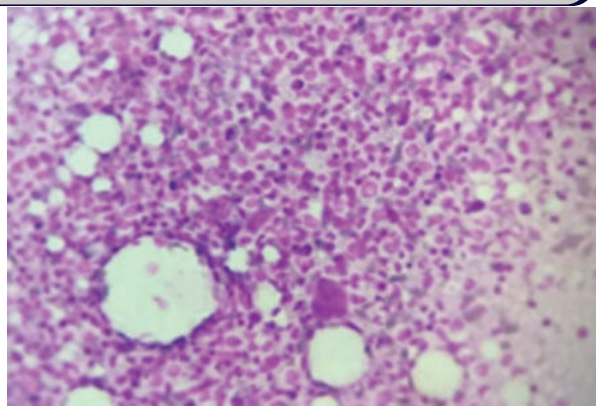
KEYWORDS : Chronic-Phase Myeloid Leukemia, Therapy Related Myeloid Neoplasms, Breast Cancer.

INTRODUCTION

Secondary leukemias that develop after treatment for carcinoma breast are mostly acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS). There is a 1% to 5% lifetime risk of developing therapy-related myeloid neoplasms (t-MN) after breast cancer treatment [1].Chronic myeloid leukemia (CML) accounts for a small percentage of these secondary leukemias.

Case Study

A 43-year-old perimenopausal woman presented with left abdominal discomfort, early satiety and anorexia of 3 months duration. She had pallor and massive splenomegaly. Her past medical history was significant for a stage II ER+/PR+ carcinoma breast seven years before this for which she was treated with surgical resection followed by 3-weekly 6 cycles of chemotherapy with 5-fluorouracil, doxorubicin and cyclophosphamide. She was on tamoxifen 20mg once daily for last 7 years. A hemogram revealed leukocytosis of 600×10^9/L, platelet count of 10×10^6/L and hemoglobin 10.4gm/dL. Peripheral blood smear showed a differential leucocyte count of 14% promyelocytes, 34% metamyelocytes, 2% metamyelocytes, 41% neutrophils and band forms,7% basophils,2% eosinophils without and blasts. This was suggestive of chronic myeloid leukemia. Bone marrow aspiration and biopsy study showed morphologic features consistent with CML in chronic phase. Molecular studies, qualitative RTPCR revealed presence of *BCR-ABL1* fusion gene[p210(e14a2&e13a2) (major)].With a final diagnosis is chronic myeloid leukemia in chronic phase with EUTOS LTS score of 117 (high risk), she was started on oral imatinib 400mg once daily.



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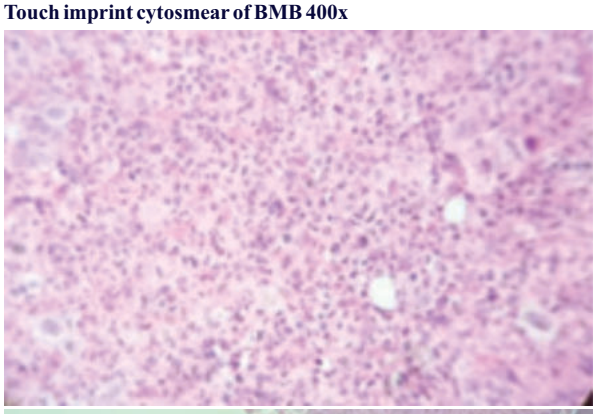
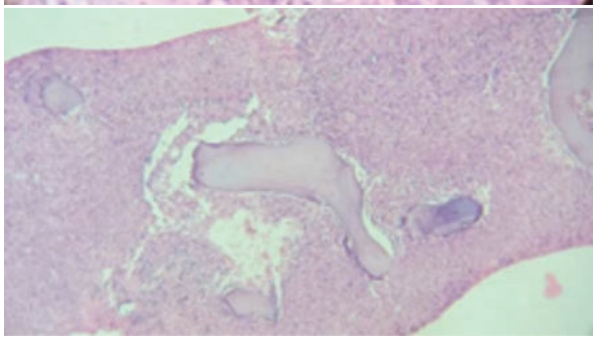
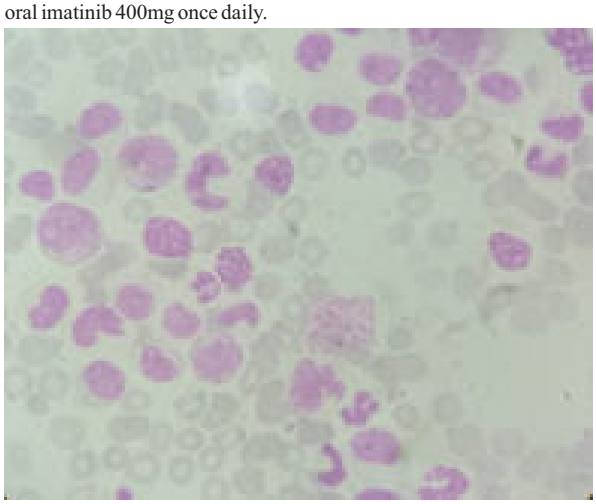
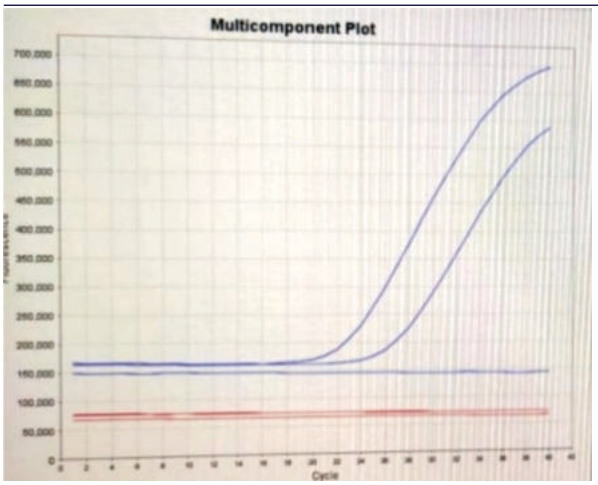




Bone marrow biopsy 400xBone marrow biopsy 100x



Peripheral Smear 1000x



BCR ABL RTPCR Qualitative [p210(e14a2&e13a2) (major)]

DISCUSSION:

Therapy for malignancies with either chemotherapy agents or radiotherapy has been shown to increase the risk of developing secondary neoplasms. In particular, the risk for myeloid neoplasms is more than 10-fold higher after chemotherapy and/or radiotherapy, with an accumulated incidence ranging from 1% to 10% depending on types of treatment[2].

The relative risk for CML in patients who have been exposed to chemotherapy and/or radiotherapy varies with different studies, ranging from 0 to 4 in the literature[3].It is not known whether a particular chemotherapy agent used for treatment of prior malignancy can be attributed to the development of CML.As for the possible mechanism of secondary CML development .There does not appear to be an obvious increase in cases of CML after treatment with chemotherapy alone. Compared to AML and MDS for which exposure to DNA-damaging medications comprise between 10-20% of cases, rates of all secondary CML appear to increase only in regimens involving radiotherapy[4]. This may be attributed to the relatively increased amount of time that the progenitor stem cells of CML spend in a quiescent phase, especially compared to the fast-replicating progenitor cells of AML and MDS[3].

Modern therapy for malignancies advocates a personalized approach, and the treatment protocols are often individualized with diversified regimens throughout the disease course. Therefore, it is difficult to identify specific regimens or agents responsible for the merging Philadelphia-positive clone and eventual development of CML. Ionizing radiation has been implicated in the development of leukemia, including CML, in patients who survived the atomic bomb in Japan. Radiotherapy has been demonstrated to have a three-fold increase in the morbidity of leukemia, with 18% being CML[5].

Radiation can be excluded as a risk factor in this patient, as she received adjuvant FAC chemotherapy, thus implicating the possible role of chemotherapy in the development of secondary CML. In a study of 15 cases of secondary CML at the Memorial Sloan-Kettering Cancer Center, New York, 12 patients received adjuvant radiation, 11 received adjuvant chemotherapy, and 15 received both therapies to the breast. The cumulative dose of anthracycline was 240 mg/m2 while that for alkylator was 4,800 mg/m2 [6]. Chemotherapeutic agents include topoisomerase II inhibitors (mitoxantrone , anthracyclines, and epipodophyllotoxins) are significantly associated with an increased risk of developing secondary leukemias. In addition, patients who receive chemotherapy or radiotherapy could possibly have their immunity impaired or bone marrow microenvironment injured. This may lead to a predisposition for secondary neoplasms via diminished immune surveillance or damaged “soil” in favor of a mutant hematopoietic clone. In contrast to therapy-related AML/MDS ,therapy- related CML demonstrates clinical outcomes similar to that of *de novo* CML[7],in line with its pathologic features and cytogenetic profile. Tyrosine kinase inhibitors (TKI) has been used as a front-line therapy in the treatment of CML-CP that developed after treatment for prior another malignancy .This patient achieved a hematological response in 4 weeks of treatment.

Secondary CML patients is comparable in terms of bcr-abl transcript, risk assessment, clinical and biological characteristics with *de novo* CML. Cytogenetic and molecular response to TKIs as well as survival are expected to be similar to *de novo* CML. Imatinib treatment is as effective in secondary CML as in *de novo* CML.

CONCLUSIONS:

This case of CML occurring 7 years after adjuvant chemotherapy for breast cancer with an anthracycline containing regimen, adds to the understanding of secondary CML . It emphasizes the importance of oncological vigilance in patients of breast cancer, for second malignancies that might be treatment induced.

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