Open Access Case Report

A Rare Case of Myelodysplastic Syndrome Presenting Synchronously with Invasive Ductal Carcinoma of the Breast

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Abstract

The presence of cytopenias in a breast cancer patient usually signify bone marrow carcinomatosis instead of an underlying myeloid neoplasm. We hereby describe a rare case of breast cancer coexisting synchronously with Myelodysplastic syndrome.

A 67 years old female presented with exertional dyspnea, pallor and breast lump. Workup revealed Stage IIIB Invasive Ductal Carcinoma Breast, estrogen and progesterone receptor positive and human epidermal growth factor receptor 2 negative. A bone marrow biopsy performed to investigate for bicytopenia showed Myelodysplastic syndrome-Increased Blasts I. The patient was treated with upfront breast surgery followed by radiation and hormonal therapy. Venetoclax was given to treat Myelodysplastic syndrome. One year post treatment patient had no evidence of breast disease and stable marrow disease.

Myeloid neoplasms rarely present synchronously with solid tumors. The management of synchronous malignancies is a challenge for treating oncologist and needs to be tailored on a case to case basis.

Keywords: Myelodysplastic syndrome, Breast neoplasms, Multiple Primary Malignancies, Synchronous malignancies, Venetoclax.

Introduction

The presence of two or more histopathologically distinct malignancies in the same individual within a period of six months are known as synchronous multiple primary malignancies.[1] The incidence of multiple primary malignancies (MPM) is reported to be between 0.7-11%; and among these synchronous malignancies constitute between 30-55% of all MPMs.[2] Among MPMs hematological malignancies are the least reported synchronously with solid tumors. Factors contributing to these MPM include genetic susceptibility, familial cancer syndromes, advanced age of the patients, depressed cellular immunity (immunosuppression produced by the first tumor), smoking, alcohol consumption, dietary patterns and low physical activity.[3]

In patients of Carcinoma Breast (CA Breast) presenting with cytopenias, the likely cause is bone marrow carcinomatosis.[4] It is very unusual that an underlying myeloid neoplasm is the cause of myelosuppression. Moreover, myeloid neoplasms (Acute Myeloid Leukemia and Myelodysplastic syndrome) in breast cancer patients are usually therapy related occurring few years post treatment instead of occurring concurrently.[5] There have been occasional case reports of concurrent acute myeloid leukemia (AML) with CA Breast[6]; however, to the best of our knowledge, no case of synchronous Myelodysplastic Syndrome (MDS) and CA Breast has been reported in literature.

This is an unusual case where Stage III Breast Carcinoma was diagnosed synchronously with Myelodysplastic syndrome-Increased blasts I. This case focuses on the importance of early and accurate diagnosis of both diseases, and a shared treatment approach between hematologist and oncologist to optimally manage both diseases in parallel.

Case Report

A 67 year old female presented to the Oncology department of INMOL Hospital, Lahore with complaints of lump in left breast for the past one year. She also had history of asthenia, exertional dyspnea and pallor for the past one year. She had received three blood transfusions in the past 6 months for low hemoglobin. No other co-morbidities were present, and her past history and family history were unremarkable for any malignancy. On examination the patient was pale and had left sided firm mobile axillary lymphadenopathy. The left breast had a hard-palpable mass approximately 5 x 5 cm, with overlying skin induration and ulceration. There was no palpable visceromegaly.

Mammography and breast ultrasonography showed BI-RADS 5 lesion. The trucut biopsy of lump revealed Invasive Ductal Carcinoma Breast grade II (Figure 1);

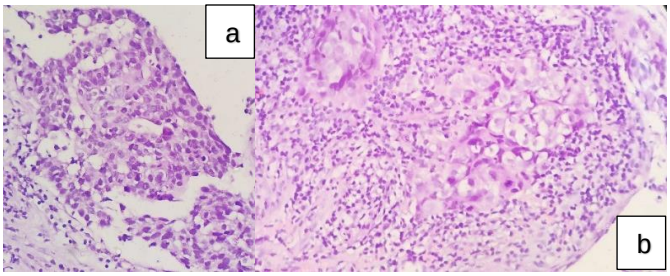

Figure 1a & b. Histopathology of Breast lump: Invasive Ductal Carcinoma.

Estrogen and Progesterone Receptor strong positive. Human epidermal growth factor receptor 2 (HER-2) was negative by FISH. Her metastatic workup was normal. Her complete blood count showed bicytopenia with a hemoglobin of 4.7 g/dl, white blood cell count (WBC) 3.4 x 10^9/L, absolute neutrophil count (ANC) 1.6 x 10^9/L and platelets 162 x 10^9/L. On peripheral smear red blood cells were normocytic and normochromic, neutrophils were dysplastic and occasional blasts could be appreciated (Figure 2).

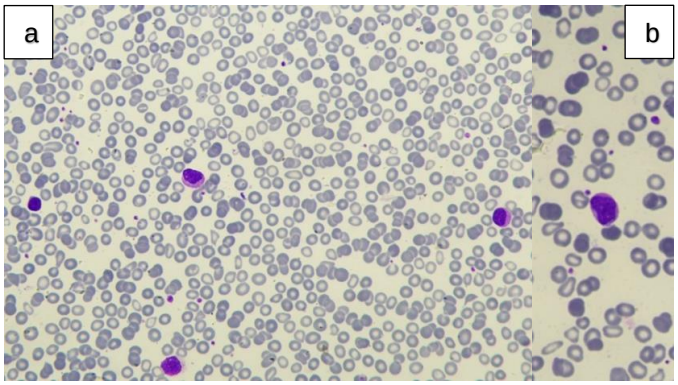

Figure 2a. Peripheral smear showing cytopenias and agranular neutrophils (20x); 2b Blast cells. (Arrow, 40x)

Case was referred to Clinical Hematology department to investigate the cause of cytopenias. A bone marrow biopsy was performed which showed reduced cellularity (20%) and multilineage dysplasia (Figure 3). Erythroid cells were megaloblastic with binucleate forms. Granulocytes showed maturation arrest and dysplasia. Megakaryocytes were dysplastic and hypolobated. Blasts constituted 8% of nucleated marrow cells and were MPO, CD34 and CD117 positive (Figure 4). Cytogenetics were normal (46 XX). 17p deletion/TP53 mutation was negative by FISH. Patient had intermediate risk MDS with IPSS-R score 4.5 and age adjusted risk (IPSS-RA): 4.42.

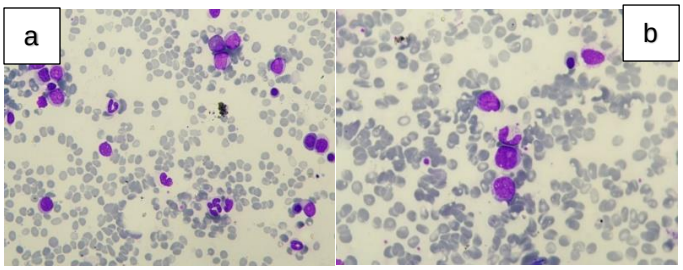

Fig.3a & 3b Bone Marrow Aspirate showing Multilineage Dysplasia and Increased Blasts. (40x)

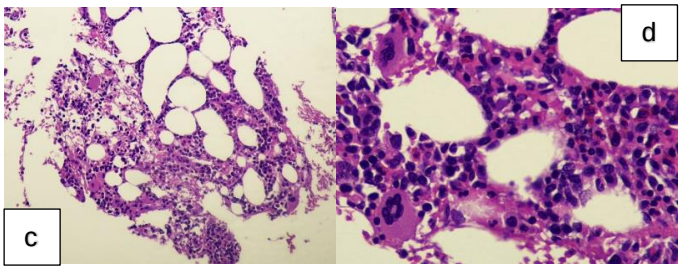

Fig.3c & 3d Bone Marrow Trephine with dysplastic megakaryocytes and increased interstitial blasts.

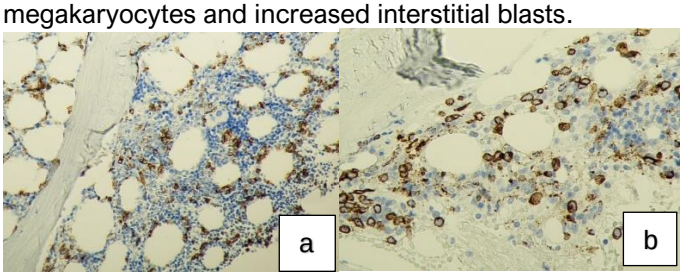

Figure 4a. Immunohistochemistry CD117 (20x) Fig.4b Immunohistochemistry CD34. (20x)

It was concluded that it's a case of Myelodysplastic Syndrome-Increased Blasts I (Intermediate Risk) with concurrent CA- Breast Stage III (T4b N1 M0).

Important considerations for treatment were the patient's age, presence of synchronous malignancies, cytopenias, prognosis of both diseases, financial status and patient wishes to avoid chemotherapy. So, a multidisciplinary tumor board with Clinical Hematologist, Medical Oncologists and Radiation Oncologists discussed possible treatment options for both malignancies. After patient counselling and informed consent, the patient underwent Upfront Modified Radical Mastectomy and axillary lymph node dissection. Post-surgery, margins were negative and 10/10 lymph nodes were positive. This was followed by radiation therapy (40Gy/15 fractions) and hormonal therapy (Anastrozole 1mg daily). For Myelodysplastic syndrome patient was advised Hypomethylating agents with Venetoclax but patient

refused chemotherapy. Therefore, Venetoclax monotherapy was continued for 6 months and then repeat bone marrow biopsy was advised.

Post 6 months treatment, patient was asymptomatic, transfusion independent and with WBC 3.5 x 10^9/L, ANC 2.1 x 10^9/L, Hemoglobin 8.6 g/dl and platelets 159 x 10^9/L. Peripheral smear showed no dysplasia and no atypical cells. On repeat bone marrow biopsy dysplasia persisted in erythroid and myeloid lineages and blasts were still 8% of nucleated marrow cells. Patient was again offered hypomethylating agent in combination with Venetoclax but again refused chemotherapy so Venetoclax was continued for an indefinite period. At the end of 1 year patient was asymptomatic, with no evidence of breast disease, transfusion independent and blood counts within normal limits. There were 7% blasts in bone marrow.

There was a loss to follow up for two months where patient discontinued Venetoclax on their own accord. She later presented with melena, weakness, lethargy and high grade fever. Performance status of the patient had deteriorated to ECOG 3. CBC showed Hb 3.6 g/dl, platelets 14 x 10^9/L and leucocytes 1.0 x 10^9/L. Repeat bone marrow biopsy showed disease progression to MDS-IB II with 16% blasts on bone marrow aspirate and trilineage dysplasia. Patient opted for palliative care and received one cycle of low dose cytarabine along with Venetoclax. However, post chemotherapy she developed severe melena, sepsis and died.

Discussion

The co-existence of two malignancies in a patient is a rare occurrence. They are called synchronous multiple primary tumors if these histopathologically distinct tumors occur within a period of six months and fulfill the criteria established by Warren and Gates.[7] After extensive literature review very few case reports of breast cancer with synchronous hematological malignancies have been found. These include cases with co-existing Chronic Lymphocytic Leukemia, AML and myeloid sarcoma.[8] Development of myeloid neoplasms post chemotherapy or radiotherapy in breast cancer is a known occurrence. This is therapy related being attributed to chemotherapeutic agents, radiotherapy and granulocyte colony stimulating factors. However, patients developing synchronous breast carcinoma with myeloid neoplasms without receiving any prior treatment is rare. This case is very unusual due to two reasons: the presence of synchronous MDS instead of being therapy related (probably the first case reported so far); and the cause of cytopenias being MDS and not bone marrow carcinomatosis.

There are certain genetic and chromosomal mutations that occur both in CA Breast and AML and may contribute to their co-occurrence. These include p53 mutation, chromosome 11 mutations, mutation in the BRCA-1 gene etc.[9] Similar genetic mechanisms might play a role in MDS co-existing with CA Breast, though further studies are required in this regard.

The management of dual malignancies is challenging and needs to be tailored on a case to case basis. The patients are more prone to infections and immune dysfunction and have lower rates of responses and survival. The challenges of managing these dual malignancies include establishing an appropriate diagnosis; determining whether both malignancies can be treated at the same time; if not how to prioritize treatment; and then selecting the most appropriate treatment options. A multidisciplinary tumor board is extremely important to overcome specialty bias and deciding on the best possible approach to patient management. In a resource limited setting like Pakistan patient compliance, their access to specialized oncological facilities, financial constraints, the lack of a proper health insurance system and patient wishes also influence treatment given and patient's outcome.

In cases of CA Breast with myeloid malignancies the treatment of breast cancer is put on hold and treatment of myeloid malignancies prioritized considering the aggressive nature of disease. However, our team decided to treat both malignancies in parallel. Chemotherapy for breast cancer was not possible due to cytopenias. So, disease was managed by surgery followed by radiation therapy and hormonal therapy. We wanted to give Venetoclax in combination with hypomethylating agents (HMA) for management of MDS. However, patient refused due to myths and fear associated with chemotherapy. Therefore, Venetoclax monotherapy was administered to control progression of MDS.

Currently approved therapies for MDS include hypomethylating agents and allogeneic stem cell

transplant. Venetoclax is an inhibitor of the anti-apoptotic protein B-cell lymphoma 2 (BCL2). Leukemic stem cells are dependent on BCL2 for survival, and inhibition by Venetoclax can lead to rapid initiation of apoptotic cell death.[10] Therefore, Venetoclax was granted accelerated approval by FDA in combination with HMA for intermediate and high risk MDS and AML and induce rapid responses and improved survival in AML/high risk MDS patients. As a single agent, Venetoclax in AML and MDS shows a tolerable toxicity profile but lower response rates.[11] Even though combination chemotherapy is preferred approach, the use of Venetoclax monotherapy has resulted in durable responses in certain situations especially in patients refractory to HMA.[12] Our case demonstrates that till the time patient was taking Venetoclax, patient remained transfusion independent and asymptomatic thus halting disease progression and leading to improved quality of life.

Conclusion

This case highlights the importance of an accurate diagnostic assessment of any unexplained cytopenia in patients with solid neoplasia. Even though standard treatment guidelines for multiple primary malignancies don't exist, a multidisciplinary tumor board discussion can help in deciding timely and appropriate interventions for both diseases involved. Patient compliance and provision of appropriate health resources remain limiting factors in lower and middle income countries in improving morbidity and mortality due to synchronous malignancies.

Declaration of Patient Consent: 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.

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