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De-novo acute myeloid leukemia in a BRCA positive female with locally treated ductal carcinoma In Situ

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ABSTRACT

Acute myeloid leukemia (AML) is primarily a disease of older adults and can arise de novo, in relation to previous treatment or in the setting of underlying hematological disease. While it is known to arise from chemoradiation in the setting of breast cancer, little is known about the association between BRCA carriers and AML. We report a case of a young female BRCA carrier who develops de novo AML without prior chemoradiation treatment, and examine if there is a link between BRCA and developing leukemia.

1. Case presentation and discussion

A 52-year-old female presented to the emergency department with complaints of fatigue, intermittent dyspnea and abdominal pain for one week's duration. Patient had undergone bilateral nipple-sparing mastectomy as well as laparoscopic bilateral salpingo-oophorectomy (BSO) one month before presentation after she was found to be BRCA2 positive 14 months prior.

A diagnostic mammogram with ultrasound 16 months prior to presentation demonstrated a 0.6 cm x 0.6 cm x 0.3 cm cluster of oval cysts at 6 o'clock anterior depth, as well as 0.6 cm x 0.8 cm x 0.3 cm oval cyst at 10 o'clock in the retroareolar region. She then underwent stereotactic-guided biopsy of the right breast that was significant for ductal carcinoma in situ (DCIS), nuclear grade 2, with multiple foci of necrosis and associated microcalcifications (Fig. 1). The DCIS was 100% estrogen receptor/75% progesterone receptor positive. 15 months prior to presentation she underwent right breast wireless localized lumpectomy, which histologically showed benign breast tissue with previous biopsy site changes. Residual ductal carcinoma was not identified and surgical margins were free of malignancy. Pathology from the bilateral mastectomy and BSO was negative for malignancy.

At current presentation in the emergency department, patient was febrile to 38.3 °C (normal range 35.8–37.9), heart rate of 110 (55–90), respiratory rate of 18 (12–16), blood pressure 126/85 mmHg, with oxygen saturation of 96% on room air. Complete blood count was significant for white blood cells of 60.6 (4.2–11.0), hemoglobin of 9.2 (12.0–15.5) with mean corpuscular volume of 101.1 (78.0–100.0), and platelets of 17 (140–450), and the differential included 84% blasts. CT scan of her chest, abdomen, and pelvis was remarkable for new splenomegaly to 17.8 cm. Blood cultures were negative for bacterial infection.

Patient subsequently underwent bone marrow biopsy showing hypercellularity and extensive infiltration by sheets of primitive blasts, the majority of which had round nuclei with prominent nucleoli (Fig. 2). Blasts compromised >80% of total bone marrow cellularity. They were positive for CD13, CD15, CD34, CD45, CD117, MPO and HLA-DR.. Fluorescence immunohistochemistry (FISH) was negative for t (15;17) *PML/RARA* rearrangement as well as t (9;22) and t (8;21). All cells featured an inversion (inv) of chromosome 16 with *CBFB-MYH11* (16q22) gene rearrangement by FISH, and a missense mutation in *KIT* was reported on next generation sequencing. 60 percent of cells cultured from the bone marrow specimen demonstrated loss of 7q and 17p, while 20 percent had a gain in chromosome 8. Patient was diagnosed with acute myeloid leukemia (AML) with inv(16). She subsequently underwent 7 + 3 induction chemotherapy with cytarabine and daunorubicin, and repeat bone marrow biopsy two weeks are completion of chemotherapy had no morphologic evidence of residual leukemic blasts. She continued to be neutropenic but transfusion independent by the time of

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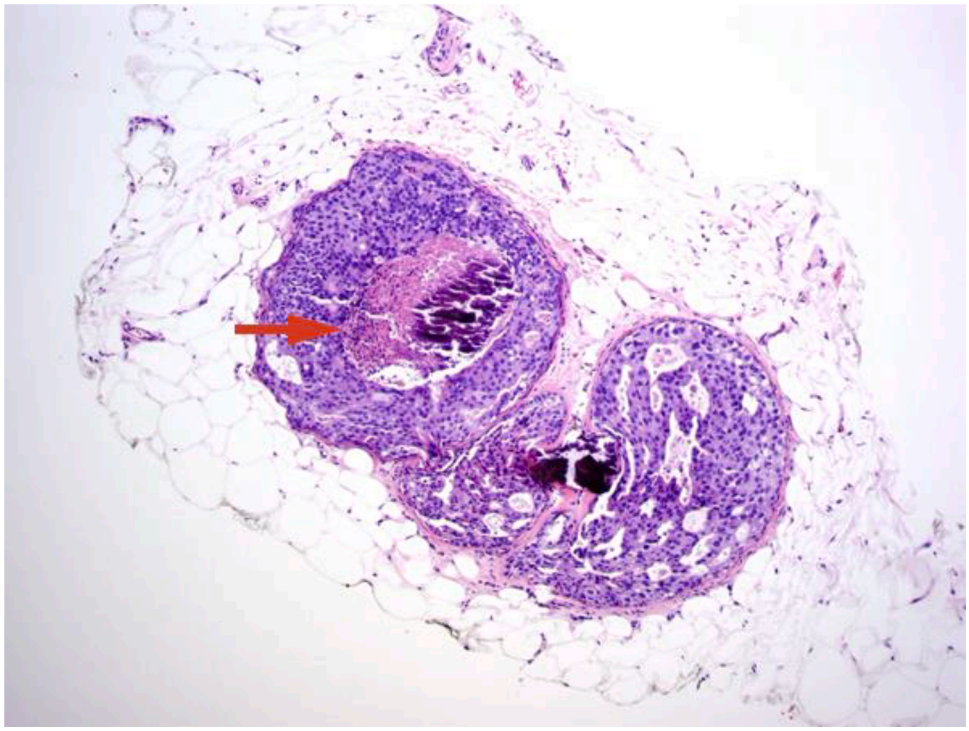

Fig. 1. DCIS demonstrated on breast biopsy. Demonstration of ductal carcinoma in situ with foci of necrosis and microcalcification (arrow).

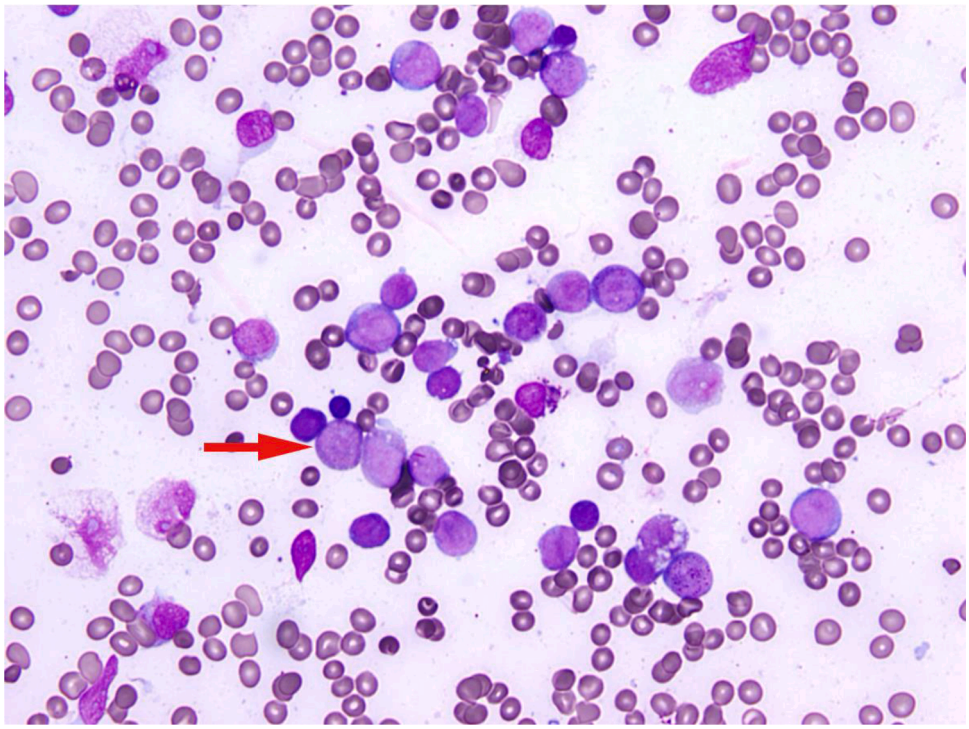

Fig. 2. Blast cells on bone marrow biopsy. Immature looking cells (arrow) much larger than the adjacent red blood cell, with scant amount of cytoplasm and prominent nucleoli with punched out appearance.

hospital discharge. Patient was discharged with plans to follow up at another institution for evaluation of a stem cell transplant.

AML is the most common acute leukemia in adults, and while it can arise in patients with an underlying hematological disorder or as a consequence of prior therapy, the majority of cases appear as a *de novo* malignancy in previously health individuals [1]. It is primarily a disease of older adults with a median age of 70 years [2]. Non-random chromosomal abnormalities, including translocations, are identified in more than half of all adult primary AML patients [3]. Of the 7 World Health Organization subtypes defined for AML in 2008, inv (16) is associated with the M4Eo subtype, M2, and M5 subtypes as well as in patients with morphological features of higher risk MDS [3,4]. 10-year survival rates

of 55% have been reported in patients with inv (16), and this mutation generally confers a favorable risk group for patients on its own unless associated with additional mutations [3,4].

Historically it has not been clear as to what extent a mutation in the BRCA genes confers risk of leukemia for women. The BRCA1 and BRCA2 tumor suppressor genes repair DNA damage to prevent tumor development, and carry a lifetime risk of developing breast cancer and ovarian cancer of up to 84% and 39%, respectively [5]. Regardless of BRCA status, a cohort of over 430,000 women from the French National Health Data System analyzed in 2019 showed that 509 cases of AML developed over a period of 10 years, and AML developed on average 2.4 years after breast cancer diagnosis (95% CI, 1.4–4.0) [6]. These women had treatment including surgical procedures, radiation therapy, chemotherapy, hormonal therapy and growth factors and it was unclear if any specifically had only surgical treatment without other intervention [6]. While cytotoxic chemotherapy for breast cancer is known to increase risk of treatment-related myeloid neoplasms, there is some data supporting an association between the BRCA mutations and leukemia development.

The Breast Cancer Linkage Consortium first reported in 1999 that relative to non-carriers and subjects with an unknown mutation status, the relative risk of leukemia in probably carriers of the BRCA2 mutation was 1.12 for both sexes (95% CI: 0.3–4.25) [7]. Friedenson et al. theorized that inactivation of any component within the pathway containing BRCA1/BRCA2 proteins would increase the risk for leukemias due to inactivation of an error-free repair process for double-stranded DNA repair [8]. Specifically, this study referenced a case series of 112 *de novo* and 21 therapy-related AML patients where 32% and 75%, respectively, had BRCA1 inactivation [8]. Iqbal et al's 2016 prospective cohort of 7243 women with BRCA1 or 2 mutation followed over a median time of 6.1 years showed that 4 women aged 34–52 developed AML with BRCA mutation, two of which were AML with BRCA2 mutation [9]. It is important to note that both of these two women had received at least surgery and chemotherapy and that one also received radiation, Tamoxifen and Letrozole. This study importantly noted that despite a higher risk overall of developing leukemia in BRCA2 carriers, the low actual risk should not influence choice of chemotherapy [9]. In both Friedenson et al.'s and Iqbal et al.'s reports, information specifically regarding genetics of the leukemic patients is not available, and therefore a correlation cannot be made with inv (16) or potential favorable prognosis.

While there is some data showing correlation between BRCA mutational status and AML, case series have been retrospective to this point. Prospective studies with BRCA patients, specifically those with only surgical intervention and not systemic treatment, to monitor for developing of leukemias is needed for further understanding of a potential link between the two. An established association has the potential to affect surveillance and treatment of this patient cohort.

Declaration of Competing Interest

All authors report no conflict of interest in submission of this paper.

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