Clinical Oncology: Case Reports

Case Report

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Treatment-Related Myelodysplastic Syndrome in a Breast Cancer Survivor with TP53 Mosaicism: The Genetic Dilemma

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Abstract

Background: Breast cancer patients commonly undergo germline genetic testing to screen for pathogenic variants in cancer susceptibility genes. When detected, pathogenic variants justify augmented tumour surveillance and family counselling. We present a case of somatic TP53 mosaicism in a patient with breast cancer who developed treatment-related Myelodysplastic Syndrome (MDS).

Case Report: An 84-year-old woman with an extensive family history of cancer was diagnosed with breast cancer. On germline genetic testing, she was found to have a mosaic TP53 mutation. A healthy skin biopsy was negative for TP53 pathologic variants. The patient declined bone marrow biopsy to exclude clonal hematopoiesis progressing to MDS, agreeing only to periodic surveillance. Three years later, she was diagnosed with treatment-related MDS, which was refractory to standard therapies. She died less than one month after diagnosis.

Conclusion: Our case demonstrates the challenges associated with identifying the clinical significance of mosaic TP53 mutation and highlights the importance of proper cancer surveillance in this patient population.

Keywords: Genes; p53; Mosaicism; Myelodysplastic Syndromes; Breast Neoplasms.

Background

Germline testing for cancer-susceptibility genes has become routine in breast cancer patients. Identification of pathogenic variants in cancer susceptibility genes has significant clinical implications but carries challenges associated with distinguishing germ line mutations from somatic mosaicism and clonal hematopoiesis. One of the most common mutations in breast cancer patients is TP53 PV, which is implicated in the development of various cancers [1-3]. Detected on germline testing, it may signify germline TP53 mutation associated with Li-Fraumeni Syndrome (LFS), somatic mosaicism related to post-zygotic changes, or acquired clonal hematopoiesis. Proper diagnosis requires thorough genetic evaluation and will significantly affect further management, including cancer surveillance and family counselling. Here, we present a challenging diagnostic case of somatic TP53 mosaicism in a patient with breast cancer who developed treatment-related Myelodysplastic Syndrome (MDS).

Case Report

An 84-year-old female patient was diagnosed with stage IA ER/PR negative, HER2 positive breast cancer and underwent adjuvant chemotherapy with paclitaxel and trastuzumab followed by adjuvant radiation. Due to an extensive family history of breast cancer in three second-degree relatives and colon cancer and oesophagal cancer in first-degree relatives, she underwent comprehensive cancer panel testing which revealed a mosaic TP53 mutation. A subsequent healthy skin biopsy revealed no PVs in the cancer-susceptibility genes. The genetic counsellor concluded that these findings may be attributed either to clonal expansion secondary to age-related changes, underlying hematologic malignancy, or classic somatic TP53 mosaicism. The patient denied a bone marrow biopsy and agreed to periodic oncology surveillance. Three years later, she presented to the emergency department with a 2-week history of generalized weakness, shortness of breath, and difficulty ambulating due to fatigue. She also complained of decreased appetite and an unintentional 30 lb. weight loss. On presentation, she was tachypneic with a respiratory rate of 26 beats per minute, and was normotensive, afebrile, and saturated 100% on room air. The initial laboratory workup was significant for haemoglobin of 6.2g/dl, low reticulocyte count of 0.02%, and platelet count of 28,000 platelets/mcL. A peripheral smear showed left shift, anisocytosis, and few schistocytes with no overt dysplasia. She received 1 unit of pure red blood cells in the emergency department and was admitted to the hospital with acute anaemia. Further workup revealed normal iron and total iron-binding capacity, elevated ferritin, low vitamin B12 of 114 pg/mL, and normal folic acid. Hematology/oncology was consulted for further assessment in the setting of her prior history of breast cancer and known TP53 mosaic mutation. She began treatment for B12-deficient anaemia and underwent a bone marrow biopsy due to concerns for underlying MDS. The results of the bone marrow biopsy were suspicious for MDS, with 1% of blasts. Cytogenetic revealed a complex karyotype, including 5q deletion and 6q deletion, consistent with therapy-related MDS. Her International Progression Scoring System (IPSS) score predicted her median survival to be less than 6 months. The patient was referred to hospice and died less than a month later.

Discussion

The TP53 gene mutation is one of the most common genetic abnormalities, with an estimated prevalence from 1 in 5,000 to 1 in 20,000 in the general population [1, 2]. The TP53 gene is located on chromosome 17, which encodes the p53 protein, a tumour suppressor gene responsible for cell cycle arrest in the setting of cell damage. The p53 pathway is activated in response to DNA damage and initiates the process of cell cycle arrest and delay at cell cycle checkpoints [4, 5].

When inherited or acquired in pre-zygotic stages of development, germline TP53 mutation constitutes the Li-Fraumeni syndrome,

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a genetic disorder manifesting at an early age with a variety of solid malignancies [6]. Acquired somatic mutations which occur in the post-zygotic stages of development can be clinically hard to distinguish from classic Li-Fraumeni syndrome. The clinical picture includes the development of various cancers including breast cancer, myelodysplastic syndromes, and sarcomas, among others. Since less than 20% of Li-Fraumeni syndrome cases are attributable to non-classic TP53 mutations, including mosaicism, somatic TP53 gene mutations, when discovered, usually require additional genetic testing for confirmation and the establishment of clinical significance [7]. Somatic mosaicism may contribute to cancer development later in life, which highlights the importance of its identification and subsequent clinical surveillance [8].

Patients with certain cancer types undergo germline genetic testing to reveal pathogenic variants of commonly implicated cancer-susceptibility genes. TP53 is one of the most clinically significant genes in breast cancer patients.3 Studies indicate that 5%-8% of patients with breast cancer by the age of 30 and up to 85% of patients under the age of 60 have TP53 mutations [9, 10]. Thorough genetic investigation with next-generation sequencing enables the detection of TP53 gene mutations at a low minor allele frequency in patients with suspected mosaicism [11]. When a TP53 pathogenic variant is found through germline genetic testing, the next step is to distinguish between germline TP53 mutation, implying underlying Li-Fraumeni syndrome, and somatic mosaicism related to post-zygotic changes, and clonal expansion of one cell line. A healthy skin biopsy is usually indicated to determine the presence of TP53 mutation in tissues derived from different germ layers. The absence of TP53 gene mutation in skin tissue can make it difficult to distinguish between clonal hematopoiesis and true somatic TP53 mosaicism. To date, there are no established guidelines to assess the distribution of TP53 mutation to confirm or rule out somatic mosaicism. Patients with somatic TP53 mosaicism are not only predisposed to various cancers but are also at the risk of developing treatment-related malignancies, such as the treatment-related MDS in our patient [10, 12]. The proper protocol to distinguish somatic mosaicism from clonal hematopoiesis is under debate. Clonal hematopoiesis may be either related to age-related changes, implying clinically insignificant clonal hematopoiesis of indeterminate potential, or it can indicate an underlying MDS. Therefore, in both confirmed and suspected somatic mosaicism, early clinical surveillance, cancer risk stratification, and appropriate family counselling are warranted.

TP53 gene mutations are seen in 28% to 38% of patients with treatment-related MDS.1 Current theory attributes the disease to increased genomic instability following wild-type p53 gene loss.13 In the setting of increased susceptibility to DNA damage, this group tends to develop MDS with complex karyotype and gene amplification [13]. Bone marrow biopsy in these patients typically reveals abnormalities of chromosomes 5 or 7, although limited data are revealing the spectrum of genetic abnormalities associated with treatment-related MDS [14]. More advanced cytogenetic abnormalities render an extremely poor prognosis due to resistance to various adjuvant chemotherapy and radiotherapy regimens. Some studies showed that a cutoff of less than 10% p53 protein expression is predictive of the development of high-risk MDS [15]. Treatment-related MDS is associated with an increased risk of death in younger patients who achieved complete remission, and an increased risk of relapse in older patients [14].

Treatment-related MDS heralds a poor prognosis, with life expectancy usually less than a year, and classic chemotherapy or hypomethylating agents provide no substantial increase in survival [16]. To date, the only therapy which shows potential for complete remission is allogeneic hematopoietic cell transplantation [17]. Due to limited life expectancy and poor prognosis, the palliative care team is usually involved, as was the case with our patient, who refused active intervention.

Conclusion

Defining the clinical significance of TP53 pathologic variants found during genetic testing in patients with breast malignancies may be challenging. Additional genetic tests including healthy skin biopsy are usually required to distinguish between germline mutation leading to Li-Fraumeni syndrome, somatic mosaicism predisposing to various cancers development, and clonal hematopoiesis. Distinguishing between somatic mosaicism and clonal cell expansion remains a difficult diagnostic dilemma. Proper cancer-surveillance strategies should be performed in any breast cancer patient with suspected TP53 mosaicism.

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