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Case Report

Early Onset of Subsequent Breast Cancer in a Young Woman Previously treated for Relapsed Childhood Acute Lymphoblastic Leukemia

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Abstract

Introduction: Subsequent Breast Cancer (SBC) is the most frequent malignancy among female Childhood Cancer Survivors (CCS) for which previous chest radiation ≥10Gy is the main risk factor. The clinical approach to these patients should be driven on evidence based guidelines and tailored to family history as well previous treatments. Aim: We report a case of early occurrence of SBC in a 20-year-old woman, 6 years after the end of treatment for a relapsed childhood precursor-B-cell Acute Lymphoblastic Leukemia (pB-ALL) in which a previously unrecognized cancer predisposition was documented. Methods: In our clinic, we recommend breast cancer screening to all female CCS at risk starting at an attained age of 25 years or 8 years after end of treatment, whichever occur last. Results: A 20-year-old female, previously treated with chemotherapy, total body irradiation and allogeneic hematopoietic stem cell transplantation for a relapsed pB-ALL, developed a stage IIB, estrogen and progesterone positive, BRCA negative, ductal breast cancer 6 years after the end of treatment. After quadrantectomy, the patient underwent a bilateral mastectomy to avoid radiotherapy to the breast, which might further increase her risk of cardiotoxicity due to a previously received high dose of anthracyclines. A more extensive genetic evaluation allowed documenting a constitutional, hereditary PALB2 mutation. Conclusion: This report highlights the need to perform a comprehensive cancer genetic predisposition panel at the time of primary tumor diagnosis in order to tailor subsequent malignant neoplasms screening as well their clinical management in the unfortunate case of their occurrence.

Introduction

Breast cancer is the most frequently reported subsequent malignant neoplasm among Childhood Cancer Survivors (CCS) who have an almost 10- fold increased risk of its occurrence as compared to their peers in the general population [1]. Females have the highest risk, being male breast cancer <1% of the overall reported cases [2,3]. Among CCS, the cumulative incidence of subsequent breast cancer (SBC) increases over time, being 20% at 45 years of age vs. an expected 1.2% by the same age and sex in the general population [4,5].

Radiotherapy with a threshold dose as low as ≥10 grays (Gy) to fields potentially involving the breast is considered the predominant risk factor for a SBC [6-7]. Indeed, among female CCS who received chest irradiation, their SBC cancer risk is more than 25-fold as compared to the non-irradiated ones [4].

In this population the median time from radiation to SBC is 15 to 20 years, with cases being diagnosed as early as 8 years from exposure [8]. Few reports have also reported an increased risk of SBC after doxorubicin exposure [9,10].

Based on the above information early breast cancer screening with annual mammography and/or breast Magnetic Resonance Imaging (MRI) is thus recommended by the International Guideline Harmonization Group (IGHG) only for female CCS treated with ≥ 10 Gy chest radiation [11]. The screening is recommended to be initiated at age 25 years or after 8 years from radiation, whichever occurs last.

We here report a case of an early occurrence of SBC in a 20-year-old woman, 6 years after the end of treatment for a relapsed childhood precursor-B-cell Acute Lymphoblastic Leukemia.

Case Presentation

A previously healthy 10-year-old girl was diagnosed with precursor-B-cell acute lymphoblastic leukemia (pB-ALL) and treated according to the AIEOP-LLA R-2006 protocol (NCT: 0061345) [12,13].

A complete morphologic remission (CR) was achieved on day 33 after the first induction phase, but PCR-based Minimal Residual Disease (MRD) was positive non-quantifiable after Protocol IB at day 78. The patient was than classified as with a medium risk ALL. The clinical course was uneventful and treatment was stopped after two years of treatment. Menarche occurred spontaneously during the consolidation phase of the protocol and was followed by regular menses.

At age 13.5 years, seven months after the end of treatment, a bone marrow relapse was documented which was treated according to the AIEOP LAL REC 2003 protocol. The patient obtained a second morphologic CR after the reinduction phase, and MRD negativity after the second consolidation block, 5 months after relapse. She then underwent an allogeneic matched unrelated donor Hematopoietic Stem Cell Transplantation (HSCT) conditioned with 12 Gy Total Body Irradiation (TBI), thiotepa, cyclophosphamide; Graft Versus Host Disease (GvHD) prophylaxis include antithymocyte globulin-Fresenius, short methothrexate and cyclosporine A. HSCT was complicated by acute intestinal GvHD (grade 2) treated with steroids and by CMV reactivation responsive to valganciclovir. Overall, and considering also the treatment for relapse, the patient received several anticancer drugs including alkylating agents as well anthracyclines and radiotherapy. The cumulative dose of alkylating agents, expressed as cyclophosphamide equivalent dose was 14,6 g/m2, while that of anthracyclines (doxorubicin 60 mg/m2, daunorubicin 190 mg/m2 and idarubicin 24 mg/m2) expressed as DOXO equivalent was of 354 mg/m2.

Before the HSCT, menses were blocked with gonadotropin releasing hormone agonist (triptorelin) therapy, which was interrupted after hematologic recovery, but spontaneous menses did not resume. A diagnosis of premature ovarian insufficiency with a clinical picture of hyper gonadotropic hypogonadic amenorrhea was made, and Hormonal Estroprogestinic Replacement Therapy (HRT) was initiated when the patient was 14-year-old.

Further post-transplant complications were characterized by multiple bilateral femoral avascular necrosis that required bilateral femoral prosthesis implantation two years after HSCT.

Further follow-up, during which HRT was continued, was uneventful for the following 4 years when at age 20 (9 years since ALL diagnosis, 6 years since HSCT) the patient felt a painless right breast lump localized in the upper outer quadrant. The ultrasonography led to the presumptive diagnosis of an inflamed fibroadenoma which was treated with anti-inflammatory therapy for two weeks. In absence of any improvement, a mammography was performed revealing a 1.3 cm mass with irregular borders. A fine-needle aspiration biopsy documented the presence of neoplastic cells (grade C5 according to the International Academy of Cytology - IAC - Yokohama classification); a subsequent agobiopsy lead to the diagnosis of an infiltrating ductal carcinoma (B5 according to the Non-operative Diagnosis Subgroup of the British National Health Service Breast Cancer Screening Programme NHSBSP) [14]. Estrogen and Progesterone Receptors (ER and PgR) were both positive in 75% of tumor cells, while the human epidermal Growth Factor Receptor 2 (HER2) was negative. The Ki67 proliferation marker was positively stained in 25% of cells.

A breast conserving surgery with upper right quadrantectomy and removal of sentinel lymph node was then performed and histopathological examination confirmed an invasive ductal carcinoma measuring 2.2 cm in diameter with a luminal B-like biology (grade 3). Surgical margins were tumor free, but the sentinel lymph node was positive. The tumor was then classified as stage IIB (pT2 N1mic M0).

A genetic testing for BRCA1 and BRCA2 mutations was performed on a pre-transplant blood sample which showed no pathogenic variants in the genes. According to the standard approach for stage IIB primary breast cancer, a postsurgical radiotherapy was planned. The patient then asked for a second opinion to our team and in consideration of the previous cancer history, and the high risk of late cardiac complications due to the already received high cumulative DOXO equivalent doses and chest radiotherapy (TBI) [15,16]. After shared decision with the patient the HRT was interrupted and treatment including 9 months adjuvant chemotherapy with paclitaxel and then CMF (cyclophosphamide, methotrexate, fluorouracil), followed by radical bilateral mastectomy with level I-II right axillary lymph node dissection was performed. During surgery tissue expanders were placed. The histopathological examination of the breasts as well of lymph nodes, showed absence of neoplastic infiltration. After surgery, the patient initiated standard anti-hormone therapy with an aromatase-inhibitor (exemestane) and GnRH agonist (triptorelin) which is still continuing without significant adverse effects. At age 23 she underwent plastic surgery to replace tissue expanders with breast implants.

Considering the early onset of SBC in this patient, a more extensive genetic evaluation with Next Generation Sequencing was performed using DNA from a pre-transplant peripheral blood sample. The AmpliSeq™ Comprehensive Cancer Panel (Thermo Fisher Scientific, Waltham, MA, USA) with 409 cancer and cancer-related genes was used and heterozygous pathogenic variant c.758dup(p.Ser254Ilefs*3) of the PALB2 gene was identified, with a 60% allelic frequency. The analysis was repeated also on a pre-transplant bone marrow biopsy (see annex 1 for details) and the variant was confirmed thus allowing to be considered as germinal. The segregation of the variant was then proposed to other family members but only the mother, aged 53 years, agreed and the same PALB2 gene mutation was also detected.

The patient's cancer family history is reported in Figure 1. Neither breast or ovarian tumor were reported in her first-degree relatives, although a maternal great-aunt (second degree relative) had concurrent breast and ovarian cancer at age 60 years.

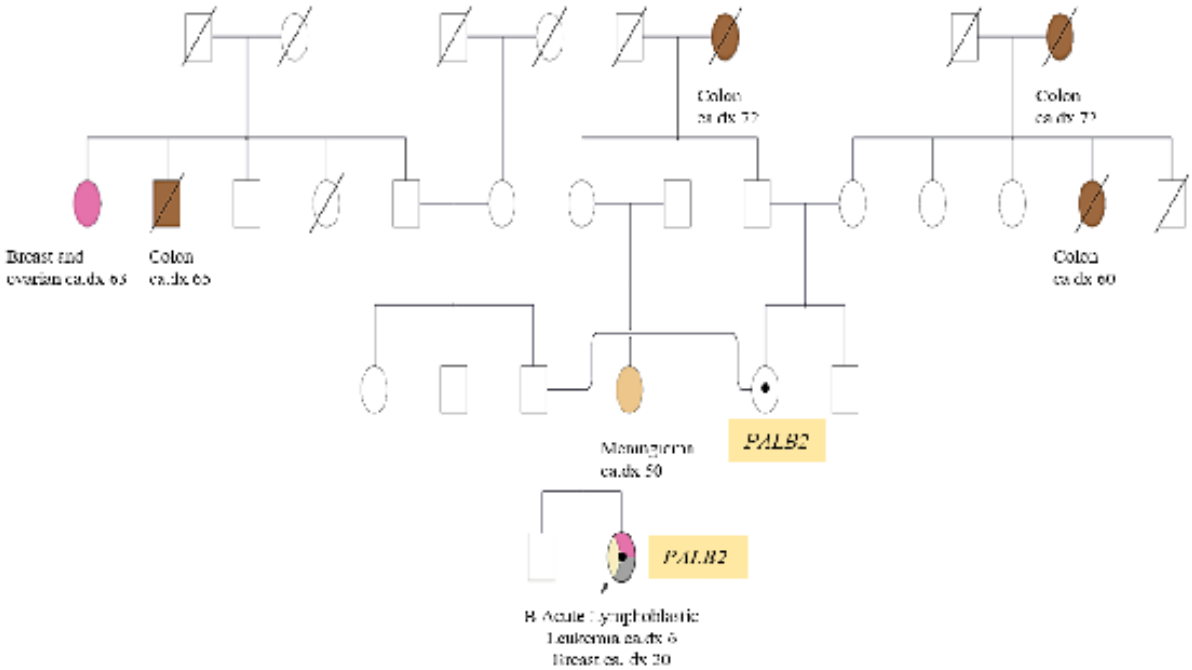

Figure 1: Pedigree chart.

As at today, 15 years after the first tumor's diagnosis and 6 years from the subsequent breast cancer, the patient is well, without any sign of tumor recurrence or cardiotoxicity. She is still under a personalized surveillance program with regular annual abdominal MRI screening, senological and gynecologic evaluation. The mother was suggested to continue her annual breast cancer screening program with mammography and the addition of breast MRI.

Discussion

To our knowledge, this patient represents one of the youngest cases reported so far of SBC occurring at a very young age (20 years) and after a very short interval (6 years) since radiotherapy exposure. A recent analysis of the St. Jude Lifetime Cohort identified 56 SBCs among 1467 CCSs which occurred at a median age of 38.6 years (range 24.5 to 53.0), with a median time since primary cancer diagnosis of 25.2 years (range, 12.7-44.6) [17].

In our patient, the SBC diagnosis was incidental since, because of her age, she was not (yet) scheduled for imaging screening with mammography and/or MRI, according to the IGHG guidelines which recommend starting at the attained age of 25 years or after 8 years after the end of treatment, whichever occurs last [11].

In this case, the main possible explanation of the SBC and of its very early onset is the previous radiotherapy exposure in a subject with PALB2 gene variant. The point pathogenic variant c.758dup (p.Ser254Ilefs*3) of the PALB2 gene is predicted to result in protein truncation or nonsense mediated decay. According to ACGM/AMP guidelines, the variant is classified as "pathogenic". The variant allele was found at a frequency of 2.4e-05 in 251366 control chromosomes; it is present in ClinVar (ID 126769) and it has been reported in the literature in individuals affected with Hereditary Breast and Ovarian Cancer Syndrome [18-19]. PALB2 loss of function mutations leads to an overall 40-60% life-time breast cancer risk, but also, for ovary cancer (3-5%) and pancreatic cancer (2-3%) [20]. Zhang et al reported that 8.5% of childhood cancer patients presents underlying genetic mutations [21] which in most patients might not be predicted by the family history. Although genetic screening in cancer patients is not routinely performed in most clinics, we believe that if it would be available even at the moment of diagnosis, it might help clinicians in tailoring front-line and salvage treatment, as well follow-up and screening.

Furthermore, this patient was also treated with 60 mg/m2 of doxorubicin and this is in line with a recent pooled analysis from six well-established studies in Europe and North America describing a dose-dependent increased risk for SBC after exposure to doxorubicin [22]. This factor might have further increased the SBC risk in this patient.

Conclusions

In our opinion, in this educational case the genetic background we documented does not correlate with the primary diagnosis of ALL for which other unknown causes should be considered. However, if a comprehensive genetic cancer panel would have been available at the moment of leukemia diagnosis and thus the information on PALB2 mutation available, the screening program could have been even further anticipated as compared to the one suggested for high-risk patients identified by the IGHG working group or a bilateral prophylactic mastectomy proposed.

Annex 1: Methods used for genetic analysis on the case report

Genomic DNA from patient's pre-transplant bone marrow biopsy was extracted using QIAsymphonyDNA Kit (Qiagen) according to the manufacturer's Targeted re-sequencing was performed using a Next Generation Sequencing (NGS) commercial cancer panel, the Ion AmpliSeq™ Comprehensive Cancer Panel (Thermo Fisher Scientific), which consisted of 409 key cancer-related genes. This panel comprises 16,000 primer pairs in four primer pools, which covers approximately 15,749 somatic mutations reported in the Catalogue of Somatic Mutations in Cancer (COSMIC). Libraries were prepared starting from 10 ng of genomic DNA using the AmpliSeq Library Kit 2.0 (Life Technologies), according to the manufacturer instructions. Final concentration of the library was evaluated with a Qubit® 2.0 Fluorometer using the Agilent High Sensitivity DNA Kit (Life Technologies). Template preparation and chip loading were performed on the Ion Chef System (Thermo Fisher). The sequencing were performed on the Gene Studio S5 (Thermo Fisher Scientific, Inc.) using 520 Ion Chip. Base calling was generated by Torrent Suite 3.0 software (Thermo Fisher Scientific, Inc.), using tmap-f3 on the Ion Torrent server for further analysis. Bam files were analyzed by the Ion Reporter Software v.5.16 (https://ionreporter.thermofisher.com/ir/) using the AmpliSeq CCP w1.2–single sample pipeline. Human genome build 19 was used as reference in alignment. To reduce the number of false positive calls, and obtain a list of confident somatic mutations we discarded variants passing at least one of the following filters: (i) phred quality score < 30; (ii) strand bias p-value < 0.01; (iii) number of variant-supporting reads < 10; (iv) variant allelic frequency (VAF) < 5% and depth < 300×; (v) allele frequency ≥ 1% in the 1000 Genomes Project European population or Exact non-Finnish European population; vi) non-exonic, non-splicing, and synonymous variants; vii) variants classified as benign in ClinVar or HGMD. The COSMIC database (http://cancer.sanger.ac.uk/cosmic) was consulted for the classification as either pathogenic, presumed pathogenic or 'variant of unknown significance.' The potential damaging effect at protein level of

missense variants were also assessed using prediction software such as SIFT, PolyPhen2, CADD, Mutation Taster, Mutation Assessor.

Genomic pre-transplant blood DNA was used for validation of the PALB2 frameshift c.758dupvariant. Exon 4 of PALB2(NM_024675.4) gene was amplified with the Platinum PCR SuperMix High Fidelity kit (Invitrogen, ThermoFisher Scientific, Waltham, MA, USA) using the following forward 5'-CCAGTTACAGAAATTAATGAAG-3' and reverse 5'-GGTTATCTGTAGAGACAGTC-3' primers (NM_ NM_024675.4). The PCR product was purified using the GenUP Exo SAP kit (Biotech Rabbit, Berlin, Germany) and amplified for Sanger sequencing by the Big Dye Terminator Circle Sequencing kit (Applied Bio systems, Foster City, CA, USA).

Ethical Considerations

Written informed consent was obtained from the patient for the publication of this report.

Conflicts of Interests

The authors declare no conflicts of interest regarding the publication of this paper. All authors have contributed to the writing and approval of the manuscript. Matteo Lambertini reports advisory role for Roche, Lilly, Novartis, Astrazeneca, Pfizer, Seagen, Gilead, MSD and Exact Sciences and speaker honoraria from Roche, Lilly, Novartis, Pfizer, Sandoz, Libbs, Daiichi Sankyo, Knight and Takeda, Travel Grants from Gilead and Daiichi Sankyo, and research support (to the Institution) from Gilead outside the submitted work

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