Donor-derived breast cancer in a bone marrow transplantation recipient

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PRECLINICAL STUDY

Donor-derived breast cancer in a bone marrow transplantation recipient

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Abstract We present the case of a young lady who had been treated for acute myelocytic leukemia at the age of 14 by means of allogeneic bone marrow transplantation, the donor being her sister. At the age of 28 she underwent modified radical mastectomy for invasive breast adenocarcinoma. Genetic analysis revealed chimeric cellular populations on both the tumour and normal tissues of the patient with preponderance of donor-derived cells. We conclude that the patient's epithelia had been repopulated by donor-derived hemopoietic stem cells which gave rise to a malignant mammary neoplasm several years later. The donor remains healthy to date. This case adds weight to the theory of pluripotent normal and neoplastic stem cell histogenesis and emphasizes the pivotal role of supporting host stroma in carcinogenesis.

Keywords Breast cancer · Allogenic bone marrow transplantation

Case report

We describe the case history of a female patient born in 1978 and diagnosed with acute myelocytic leukemia at the age of 14. After idarubicin/cytarabine induction chemotherapy she underwent conditioning with cyclophosphamide, alemtuzumab, and total body irradiation and received an allogeneic bone marrow graft from her HLA-matched sister. Repeated hematologic and bone-marrow examinations showed complete remission of the disease, sustained to date. In 2006, at the age of 28 years, she palpated a lump at the upper-external quadrant of the right breast. Following diagnostic work-up she underwent modified radical mastectomy and axillary node dissection. Histological examination of the specimen revealed a grade 2 adenocarcinoma of 7.5 cm maximal diameter. Eleven out of 13 resected axillary lymph nodes were involved, while estrogen/progesterone receptors and HER-2 were positive by immunohistochemistry. Staging for distant metastases was negative (AJCC stage pT3pN3M0, IIIC). The patient's sister underwent diagnostic work-up with physical examination, blood tests, chest X-ray and mammary ultrasound and was found to be healthy. Considering the history of allogeneic bone marrow transplantation, we decided to perform an appropriate DNA identity testing in order to define the genetic origin of our patient's tumor.

Genetic analysis

We compared the genetic pattern of the patient's oral epithelial cells, peripheral blood mononuclear cells and formalin-fixed paraffin-embedded neoplastic mammary cells as well as the donor's and both parents' peripheral blood mononuclear cells. For this purpose, DNA was extracted from the above samples, and an ABI AmpFlSTR commercial kit (Applied Biosystems, CA, USA) was used to simultaneously amplify 15 four-nucleotide short tandem repeat (STR) loci as well as one marker for the XY chromosomes.

The analysis of all 15 STR loci showed no major inconsistencies. As expected, the patient's peripheral blood

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mononuclear cell genetic pattern matched her sister's (donor). The results of the genetic analysis are presented in Table 1 and Fig. 1. All alleles were successfully traced to the paternal and maternal blood (germ-line) samples and were informative for most STR loci (10/15). Based on the inheritance pattern of the variant alleles, two distinct genetic patterns were observed in both the breast tumour and oral mucosa of the patient. These two patterns made up a chimeric population consisting predominantly from the donor graft and to a lesser extent, as estimated by the fluorescence intensity of each peak on the electropherogram, from the patient's germ-line lineage. For example, in the breast cancer sample and oral mucosa of the patient, alleles 13 and 14 for locus D5S818 represent the patient's germ-line lineage of paternal and maternal origin, respectively, whereas alleles 11 and 12 are derived from the donor graft. The presence of a chimeric population suggests repopulation of the patient's epithelia from the transplanted bone marrow-derived stem cells of her sister, as well as host epithelial stem cells.

Discussion

We showed that the breast tumor affecting the patient quite probably originated from donor-derived bone marrow stem cells. Consequently, one is led to hypothesize that donor hemopoietic stem cells repopulated the patient's mammary duct epithelium during allogeneic bone marrow transplantation. There is evidence that such epithelial repopulation is indeed possible and that bone marrow-derived stem cells can produce cancer in the host tissue given adecuate stimulation [1, 2]. A number of similar observations have given rise to speculation concerning a central role of bone-marrow-derived stem cells in the initiation of most epithelial cancers [3]. In fact, most studies to date concerning the role of donor-derived bone marrow stem cells in transplant recipients have relied on identification of the sex chromosomes in sex-mismatched transplants. These studies have failed to reach consistent conclusions for the origin of tumors observed in such cases [4, 5]. We relied on study of an adequate number of genetic polymorphic markers and found a chimeric, genetically mixed population in the patient's normal and neoplastic epithelia, suggesting that mucosal repopulation originated from host and donor stem cells, as expected.

Although genetic analysis was restricted to tissue sections with more than 75–90% epithelial breast cancer cells as judged by hematoxylin-eosin staining, host stromal cells probably contributed to extracted DNA. However, the prevailing tumour signature remained that of the sister. In fact, laser microdissection may have allowed us to test the possibility of epithelial reconstitution solely from donor cells. Even so, given the 75–90% percentage of tumour

Table 1 Genetic make-up of studied biological material

STR locus	Patient's blood	Patient's saliva[a]	Patient's tumor[a]	Patient's sister's blood	Patient's father's blood	Patient's mother's blood
D8S1179	8, 13	8, 13	8, 13	8, 13	13, 13	8, 14
D21S11	30, 31.2	30, 31.2/29	30, LOH[b]	30, 31.2	29, 30	30, 31.2
D7S820	8, 10	8, 10	8, 10	8, 10	10, 10	8, 10
CSF1PO	10, 11	10, 11	10, 11	10, 11	11, 11	10, 12
D3S1358	14, 18	14, 18/15	14, 18/15	14, 18	14, 16	15, 18
TH01	6, 6	6, 6/9.3	6, 6/9.3	6, 6	6, 9.3	6, 9.3
D13S317	8, 12	8, 12/11	8, 12/11	8, 12	11, 12	8, 9
D16S539	9, 9	9, 9/11, 13	9, 9/11, LOH[b]	9, 9	9, 11	9, 13
D2S1338	20, 24	20, 24/23	20/23	20, 24	23, 24	19, 20
D19S433	13, 14	13, 14/13.2	13, 14/13.2	13, 14	13, 13.2	14, 15
vWA	17, 17	17, 17/15	17, 17/15	17, 17	15, 17	15, 17
TPOX	9, 11	9, 11	11	9, 11	8, 11	9, 11
D18S51	13, 16	13, 16/15, 17	13, 16/17, LOH[b]	13, 16	15, 16	13, 17
Amelogenin	X, X	X, X	X, X	X, X	X, Y	X, X
D5S818	11, 12	11, 12/13, 14	11, 12/13, 14	11, 12	11, 14	12,13
FGA	20, 22	20, 22	20, 22	20, 22	19, 22	20, 24

The numbers in cells represent the identified variant alleles for each locus and refer to complete four base pair repeat units for each allele. For example, the D8S1179 8 and 13 alleles contain 8 and 13 complete four base pair repeat units, respectively

[a] The alleles after the dash (/) represent the patient's own genetic pattern

[b] Loss of heterozygosity probable

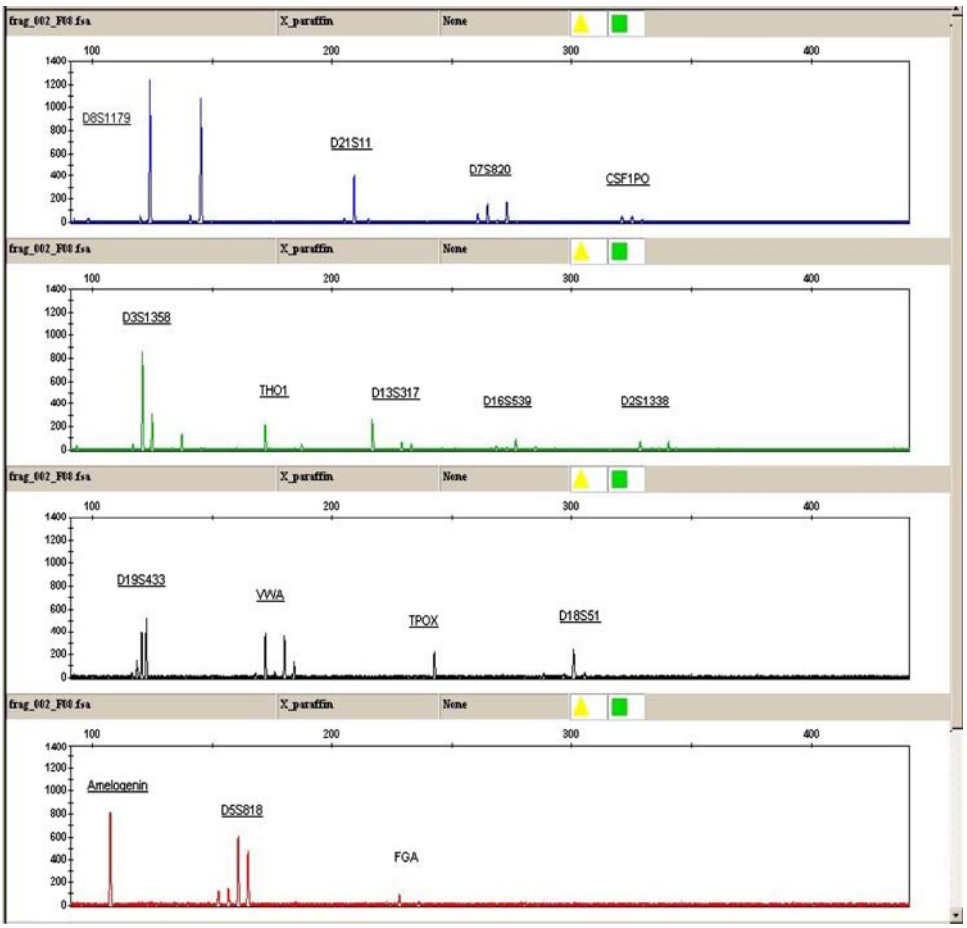

Fig. 1 Genetic pattern of the patient's tumor

epithelial cells in tissue sections analysed, we feel confident that the bulk of DNA was extracted from breast cancer cells.

Our observation, along with others, adds weight to the theory of derivation of normal and neoplastic epithelia from pluripotent stem cells and emphasizes the pivotal role of host stroma to malignant transformation. Neoplastic stem cells have been postulated to conserve self-renewal and repopulation properties in addition to possessing aberrant proliferation and genetic repair [6]. Normal-appearing host stroma was shown to modulate malignant clone emergence, proliferation and regression in preclinical models [7]. In our case, the donor who contributed the stem cell graft is healthy, while a tumour originated from this same graft in the recipient. It should be emphasized that the donor stem cells, which subsequently gave rise to the malignant clone, had not been exposed to the deleterious effects of ionising radiation or cytotoxic agents, in contrast to the host stroma and epithelia. It is possible that conditioning chemotherapy and radiotherapy administered before transplantation inflicted genetic damage to host stromal cells. Further research is needed at a basic and translational level in order to illuminate the complex and poorly understood mechanisms of stem cell growth and epithelial-stromal interactions.

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