Solid tumor transmission from donor to recipient after allogeneic stem cell transplantation: it is rare but it happens!

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INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is the only therapeutic approach with the potential to cure various hematopoietic diseases. However, long-term survivors remain at high risk of late complications, including the development of secondary solid malignancies. There is a limited amount of data regarding the cell of origin and the pathogenesis of secondary solid malignancies post allo-SCT. Several hypotheses have been proposed, such as *de novo* occurrence, progression of an occult pre-existing malignancy, and donor cell-related malignancy[1].

Here, we report a case of a secondary solid neoplasm developed post allo-SCT in a patient with acute myeloid leukemia (AML). Details of an extensive laboratory evaluation carried out to elucidate the origin of the neoplastic cells are presented.

CASE REPORT

A 56-year-old woman presented with right cervical lymphadenopathy. Biopsy of a supraclavicular lymph node revealed myeloid sarcoma. Full blood count with differential and biochemistry was normal. Bone marrow (BM) aspiration and biopsy did not reveal leukemic infiltration. Total body computed tomography (CT) scan revealed multiple minimally enlarged mediastinal and abdominal lymph nodes (max. diameter <1 cm).

The patient was treated with standard induction chemotherapy consisting of anthracycline and cytarabine followed by consolidation with high-dose cytarabine. A positron emission tomography (PET)-CT scan performed after the end of consolidation showed mild ^{18}F-fludeoxyglucose (FDG) uptake at right cervical lymph nodes, a finding suggestive of residual disease.

Allo-HSCT with the use of peripheral blood stem cells (PBSC) from a matched sibling was performed. The patient had a prompt engraftment and PET-CT scan performed two months after transplant did not reveal residual FDG uptake in previously involved sites.

During the next few weeks, the patient reported persistent lower back pain, and total body magnetic resonance imaging (MRI) revealed tumor lesions on the liver and sacral bone. A repeat PET-CT scan showed increased FDG activity in the left sacral bone (SUV-max: 3) and in the liver (SUV-max: 7) (**Figure 1 a** and **b**). The working diagnosis was relapse of AML as the liver and bone lesions were considered to be myeloid sarcomas. A week later and at around day +130 after graft infusion, we were informed that the donor had been diagnosed with limited stage small cell lung cancer (SCLC).

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The donor, a 63-year-old male who had previously been a heavy smoker was completely asymptomatic at the time of donation. Review of donor medical records did not reveal any abnormal finding. Chest X-ray performed during the pre-transplant donor evaluation was also normal.

Soon after this, a CT-guided fine needle biopsy of the patient's liver lesion mass was performed and revealed infiltration by a small round blue cell tumor with an immunophenotype similar to her donor's neoplasm (**Figure 1 c-f**). The patient received chemotherapy for SCLC consisting of cisplatin and etoposide, but unfortunately the disease was refractory to treatment, her clinical condition deteriorated rapidly, and she passed away 3 months after the initial cancer diagnosis.

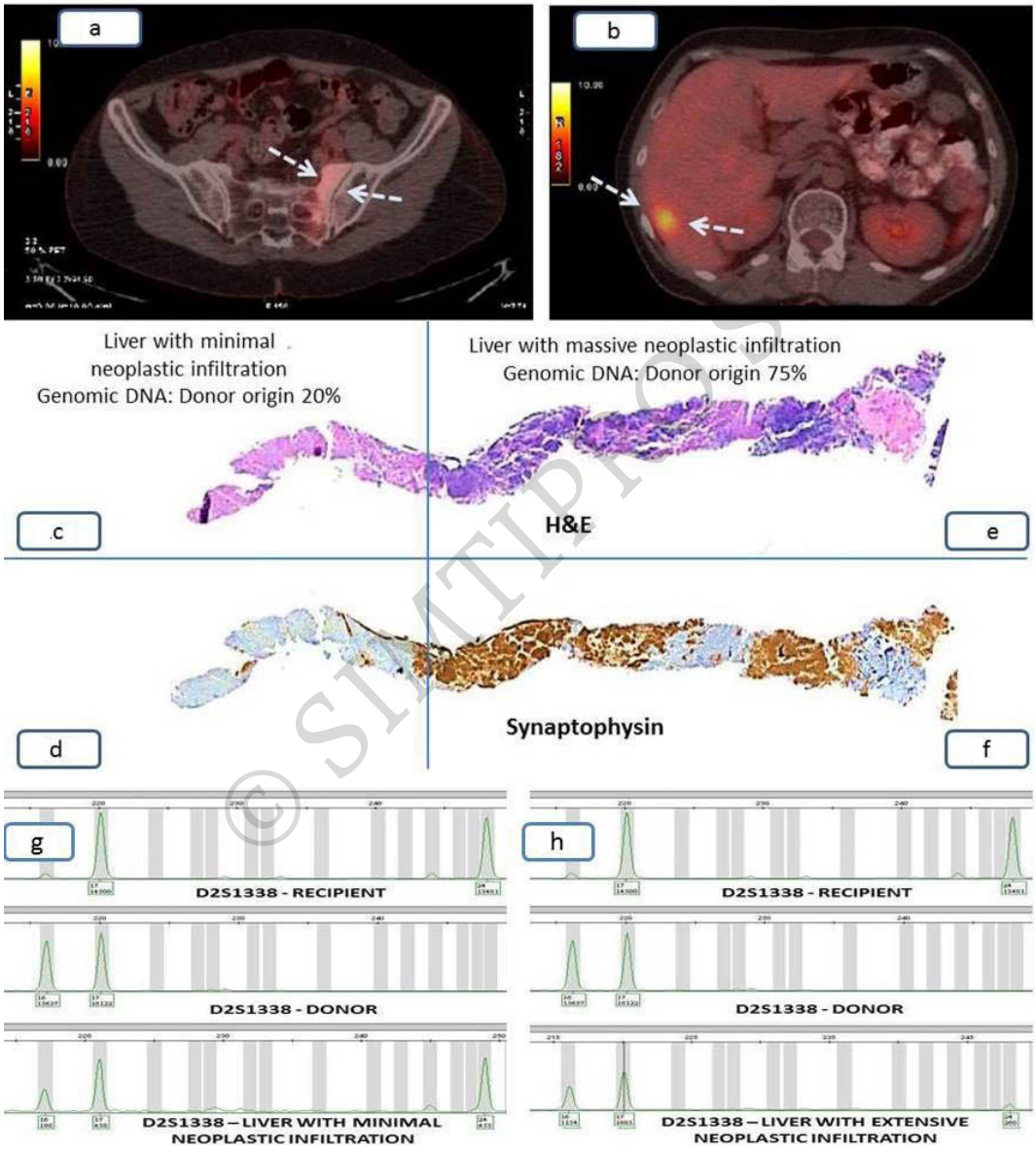


Figure 1 - PET-CT scan, biopsy and short tandem repeats (STR) markers analysis

Left sacral bone and right hepatic lesion in segment VI (arrows) are 18FDG avid (SUV-max: 3 and 7) on fused transaxial (**a** and **b**) 4 months after the allogenic transplantation. Fine needle biopsy of the hepatic lesion. Panoramic view showing minimal neoplastic infiltration of the liver parenchyma on the left (**c** and **d**) with extensive infiltration on the right (**e** and **f**) by a small round blue cell neoplasm (upper panel, **c** and **e**, H&E stain). Synaptophysin immunostain highlighting the neuroendocrine differentiation of the neoplastic infiltrate (lower panel, **d** and **f**). Fragment analysis of DNA samples, taken from tissue parts with minimal and massive neoplastic infiltration, with the use of four informative STRs markers showed that 20% and 80% of genomic DNA was of donor origin, respectively (**g** and **h**).

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The concurrent presence of the same type solid malignancy in both donor and recipient raised the possibility of cancer cell transfer through PBSC infusion. Formalin-fixed paraffin embedded material from the patient's liver tumor was available for analysis after written informed consent was given by the family of the deceased. Due to sex-mismatch between donor and recipient, interphase FISH-analysis was applied initially for the identification of sex chromosomes. FISH analysis on the neoplastic tissue showed that approximately 75% of the analyzed cells were X0 and the other 25% were XX. No signal for the centromere of chromosome Y was detected on any of the 200 cells examined. FISH analysis was considered non-informative since no conclusion could be made as to whether cells with X0 chromosome belong to the female recipient that has lost one copy of X chromosome or the male donor that has lost Y chromosome.

As a next step, we used chimerism fragment analysis as previously described[2]. Pre-transplant donor and recipient frozen DNA samples were analyzed for the identification of informative short tandem repeats (STRs) markers. DNA samples taken from different sites of paraffin-embedded liver tumor samples by using macro-dissection were analyzed. Analysis of the DNA from the part of the tissue with minimal neoplastic infiltration revealed that 80% of the genomic DNA was of recipient origin (**Figure 1 c** and **d**), whereas analysis of the same STR markers from the part of the tissue with massive neoplastic infiltration revealed that 75% of the genomic DNA was of donor origin (**Figure 1 e-h**). In conclusion, the results of fragment analysis proved the donor origin of the cancer detected in our patient.

DISCUSSION

Donor-derived tumors are a rare complication following allo-HSCT, and in the vast majority of cases are malignant neoplasms of hematopoietic origin. Although various hematological malignancies of donor origin have been detected in the recipient, donor cell AML is the most common disorder[3,4].

Although a possible explanation is the concurrent development of SCLC in both siblings, the odds against this co-occurrence are extremely high given the rarity of SCLC. If indeed this is the case, the genetic studies could be explained either by excessive donor-derived lymphocyte infiltration in the recipient's tumor (not observed in our case), by fusion of BM-derived donor cells with host tumor cells, by metaplasia of BM cells to tumor cells, or by horizontal transfer of donor-derived DNA to newly developed host cancer cells[5-7]. These mechanisms have been suggested to explain the frequently observed epithelial cells of donor origin or the development of donor-derived oral squamous cell carcinoma after allo-HSCT[8,9].

A study performed by the Australasian BMT Working Group examined the contribution of donor BM-derived cells (BMDCs) to the development of skin and gastrointestinal cancer in recipients after allo-SCT. Laboratory evaluation of tumor samples failed to detect neoplastic cells of donor origin. However, in cases of gastrointestinal neoplasia, a percentage of tumor-associated myofibroblasts were of donor origin, suggesting the direct differentiation from donor BMDCs infused with the graft, such as mesenchymal stem cells (MSCs)[10].

In our case, the most likely explanation for the SCLC that developed in the recipient is passive transmission of malignant cells from donor to recipient though contaminated graft. Indeed, Brugger *et al.* showed that micro-metastatic SCLC cells within the BM can be mobilized with granulocyte colony-stimulating factor into peripheral blood and contaminate the hematopoietic stem cell grafts[11,12].

To our knowledge, this is the first case reported of a solid tumor transferred from donor to recipient through a contaminated graft. Moreover, for older donors, the required testing for evaluation of donor eligibility should be re-considered.

AUTHORS' CONTRIBUTIONS

PT, AS, and PF analyzed the data and wrote the paper. MS, SC, TT, AK, DV, MG and KG collected and analyzed the data. NG and PR analyzed and interpreted the data.

Keywords: *solid tumor, allogeneic stem cell transplantation, secondary, donor origin, contaminated graft.*

The Authors declare no conflicts of interest.

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