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Case Report

Acute Leukemia Relapse after Ovarian Cortex Autograft: A Case Report

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Abstract

The management of young adults with cancer must now include the preservation of fertility. In some situations, the only option is ovarian tissue cryopreservation (OTC). Reuse by autograft offers good results, but is not always possible, or may induce a risk of relapse for pathologies with high risk of ovarian localization. Thanks to the various techniques currently available to investigate residual disease in ovarian tissue, the risk of reintroduction of malignant cells is considered low. We report here a case of acute leukemia relapse after ovarian tissue autograft. This was a patient with a diagnosis of pro B acute lymphoblastic leukemia (ALL). Before a highly gonadotoxic treatment, cryopreservation of ovarian tissue was performed. Following these cancer treatments, the patient was in persistent complete molecular remission. The carcinological and functional qualification of the ovarian cortex were favorable. After multidisciplinary agreement and as part of the DATOR protocol, ovarian cortex autograft was performed. Fourteen months after ovarian tissue autotransplantation, a relapse of ALL was diagnosed. The assessments performed are in favor of a late relapse of the patient's cells, but whose origin cannot be confirmed. The management of patients with high-risk pathologies is complex. For some of these patients, OTC and subsequent autograft is the sole treatment available. This case highlights the importance of ensuring the carcinological safety of the grafts before ovarian tissue transplantation by developing and improving residual disease investigation techniques, but also by developing alternative reuse techniques, such as folliculogenesis *in vitro* or models for ovary reconstruction.

Keywords: Case Report; Fertility Preservation; Ovarian Tissue Cryopreservation; Auto transplantation; Leukemia

Introduction

Anti-cancer therapy is often a cause of premature ovarian insufficiency and infertility; since the ovarian follicle reserve is extremely sensitive to the effects of chemotherapy and radiotherapy [1]. Ovarian tissue cryopreservation (OTC) and transplantation have emerged as a strategy for fertility preservation, especially for prepubertal girls, adolescents and women in whom cancer treatment cannot be delayed, and OTC is no longer considered experimental [2-5]. In terms of efficacy and success rates, according to some publications reporting cumulative data from several centers, around 30% of auto transplanted patients conceive and deliver with the aid of OTC [6-8].

Myeloblastic (AML) and lymphoblastic (ALL) acute leukemia are a group of life-threatening malignant disorders of the blood and bone marrow. In the adolescent and young adult (AYA) population, acute leukemias are the most prevalent cancer [9]. Overall 5-year survival among AYAs has increased since the 1970s [10].

In cases of leukemia, since standard chemotherapy protocols are devoid of alkylating agents, significant ovarian damage is unlikely. Only patients who subsequently need additional high-dose chemotherapy (for example, before allograft myeloablative therapy) are referred for OTC harvesting due to the high risk of sterilization [11].

However, in cases of cancer with a high risk of ovarian metastasis, such as leukemia, an important concern is the risk of relapse via the graft. Although the risk of reintroducing malignant cells is very low [7], it is essential to ensure the carcinological safety of the autograft, especially through the detection of minimal residual disease (MRD) in the ovarian cortex. This can be done using multicolor flow cytometry (MFC), molecular techniques and next generation sequencing, or xenografting in immunodeficient mice [11-14]. Making the decision of performing or not the graft depends on the results of carcinological and functional characterization.

We report here a case of relapse of lymphoblastic leukemia after autograft of ovarian tissue. As far as we know, no similar case has yet been published in the literature.

Case Presentation

This is the case of a 32-year-old Caucasian woman with no notable medical history. Mother of a 10-month-old baby, she carried out a systematic biological assessment in September 2012. The blood count showed neutropenia. A myelogram was performed and found marrow infiltration by 89% of lymphoblasts. The immunophenotype by MFC was $CD19^+$, $CD20^-$, $CD34^+$, $CD10^-$, and $CD123^+$. Bone marrow molecular biology analysis found VH1-JH6 and Vg4-Jg1.3/2.3 as markers. The diagnosis of ALL pro B non-hyper leukocytic was retained. The patient was treated with chemotherapy according to the GRAALL 2005 protocol (prednisone, vincristine, daunorubicin, cyclophosphamide, L asparaginase). Due to the persistence of minimal residual disease, bone marrow allograft was planned. Before a highly gonadotoxic conditioning treatment (total body irradiation and cyclophosphamide), unilateral ovariectomy for fertility preservation by cryopreservation of ovarian tissue was performed in March 2013.

Following these cancer treatments, the patient was in persistent complete molecular remission, without any sign of graft versus host disease or immunosuppressive medication. In September 2015, she expressed her desire for a new pregnancy. In view of her ovarian insufficiency (FSH level at 79 IU/L, amenorrhea and hot flashes, non-measurable antral follicular count), the reuse of cryopreserved ovarian tissue by autograft was proposed.

The carcinological qualification of the ovarian cortex was favorable. Histological analysis did not find neoplastic cells. MRD detection by MFC in cryopreserved ovarian cortex with the diagnosis markers (CD19, CD34, CD10, CD123) was negative (at the maximum threshold of $< 1x10^{-4}$). Molecular markers (VH1-JH6) was also negative (threshold 10^{-5}).

The functional qualification of the ovarian cortex was also favorable. Pathological examination documented the presence of many preantral and primordial follicles (22 follicles per 28 mm^2 of the thawed test fragment). The trypan blue viability test found 95% of live follicles after thawing.

After multidisciplinary agreement and as part of the DATOR protocol [6], ovarian cortex autograft was performed in July 2018. After 2 months, recovery of ovarian function was observed with a decrease in FSH level and the appearance of the first antral follicles at endovaginal ultrasound. Her husband's spermogram, without abnormalities, was compatible with a natural conception. As early as the 3rd month, the ultrasound and hormonal monitoring of the cycle made it possible to obtain a pregnancy 6 months after the ovarian cortex autograft. The outcome of this pregnancy was an early miscarriage.

During a follow-up myelogram in September 2019, a relapse of ALL was diagnosed. MFC found an immunophenotype close to the initial diagnosis ($CD19^+$, $CD20^-$, $CD34^+$, $CD10^-$ and $CD123^+$ low). Molecular biology revealed a clonal evolution, with presence of the Vg4-Jg1.3/2.3 marker and disappearance of the VH1-JH6 marker. The bone marrow karyotype initially corresponded to that of the donor (XY) with the presence of trisomy 8 (5 out of 20

mitoses analyzed). This anomaly was no longer highlighted on subsequent karyotypes (absence of trisomy 8 image on 50 mitoses analyzed). A pathological analysis of the grafts was not performed, as removal was deemed unnecessary.

In October 2020, the patient was in remission thanks to chemotherapy treatments inspired from EORTC protocol, with a combination of chemotherapy and blinatumomab. The complete molecular remission was obtained again; we did not performed a new transplantation, and the patient received Blinatumomab for 5 consolidation cycles. Due to her age at the end of chemotherapy, the couple gave up the project of a new child.

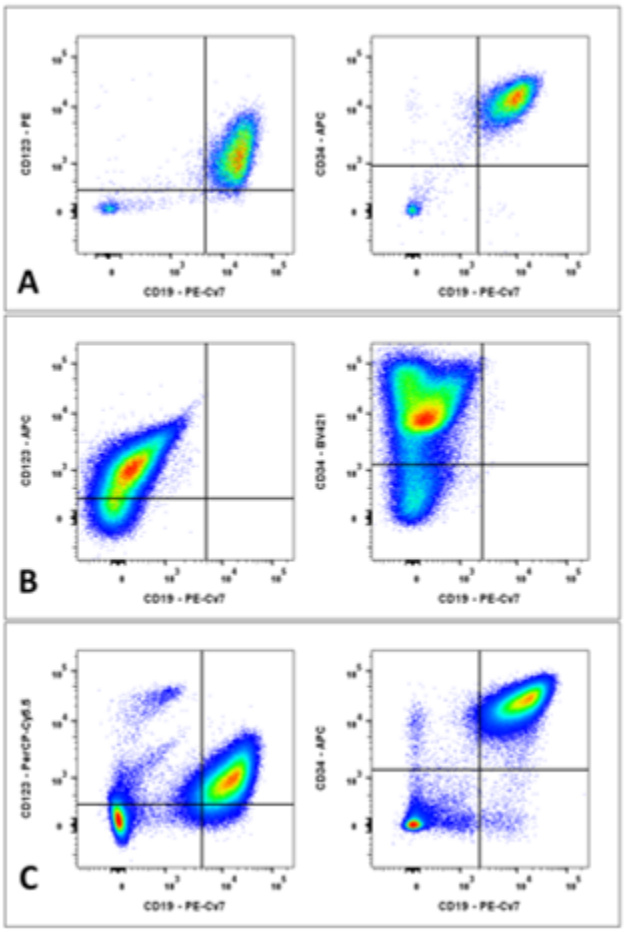

Figure 1: Comparison of multicolor flow cytometry at the time of diagnosis on bone marrow (A), at the time of MRD in ovarian tissue (B) and at the time of relapse on bone marrow (C).

	Markers in multicolor flow cytometry	Markers by molecular biology
At the time of diagnosis on bone marrow	$CD19^{+}$ $CD20^{-}$ CD34+ $CD10^{-}$ $CD123^{+}$	Vg4-Jg1.3/2.3 and VH1-JH6
MRD in ovarian tissue	CD19- CD34 - CD123 negative	VH1 JH6 negative
At the time of relapse on bone marrow	$CD19^{+}$ $CD20^{-}$ $CD34^{+}$ $CD10^{-}$ $CD123^{+low}$	Vg4-Jg1.3/2.3

Table 1: Comparison of markers investigated by flow cytometry and molecular biology.

Discussion

Hematologic cancers are the most common indication for fertility preservation, because chemotherapy, radiotherapy, surgery or a combination thereof, can induce premature ovarian insufficiency [8]. Although the risk of reintroducing malignant cells is very low [8], carcinological qualification of the ovarian cortex is essential to assess the risk of reintroducing the initial disease. To this end, several technologies can be used, including MFC [15]. Our team has demonstrated the effectiveness of MFC for the detection of MRD in ovarian cortical tissue [16,17]. However, current MRD techniques have some limitations, including the MFC detection threshold for viable leukemic cells in the ovary. Currently, the level of MRD that can induce relapse after ovarian cortical transplantation remains unknown [12]. To the best of our knowledge, this is the first reported case of a relapse of acute lymphoblastic leukemia occurring after ovarian cortex transplantation. In our case, there is the question of the origin of the relapse of the patient's ALL, namely whether it was due to relapse from the leukemic cells from the patient, leukemic transformation of the donor cells, the influence of pregnancy or possible dissemination from the fragment of ovarian cortex.

Although leukemia itself represents a common indication for OTC, transplantations are generally avoided in most fertility preservation centers, owing to the potentially high risk for disease recurrence [18]. Most often, as in our patient, OTC is performed after receiving initial chemotherapy. Recent exposure to chemotherapy (< 3 months) does not alter the chances of recovering ovarian function and becoming pregnant [19]. In addition, the literature reports cases of live births after transplantation of frozen-thawed ovarian tissue in a patients with leukemia [11,20,21]. The majority of relapses occur within 2 years of allogeneic stem cell transplantation. The patient expressed her wish to perform an autotransplant 2 years after the end of the treatment. Thus, the multidisciplinary medical team decided to postpone this treatment in order to gain some distance from the initial pathology. Most often, leukemia is discovered during pregnancy. The influence of the pregnancy itself on the occurrence of the disease is possible, probably via the immunotolerance it induces. In addition, the patient's relapse occurred at a distance from pregnancy.

Chimerism analysis on the blood revealed a mixed hematopoietic chimera, with 75% of the CD34 cell fraction coming from the recipient. MFC revealed an immunophenotyping of relapsed ALL-B (close to that of the initial disease with some modulated markers). Molecular biology analysis was positive for Vg4-Jg1.3/2.3 (same marker as at initial diagnosis) but no VH1-JH6, indicating a clonal evolution quite frequent in late relapses. In conclusion, the assessments performed are in favor of a late relapse of the patient's cells, but whose origin cannot be confirmed.

The management of patients with high-risk pathologies is complex. For some of these patients, OTC and subsequent autograft is the sole treatment available. This case highlights the importance of ensuring the carcinological safety of the grafts before ovarian tissue transplantation. Carcinological qualification techniques must be developed and optimized. Alternative techniques for the reuse of self-preserved ovarian tissue are under study, and may mitigate the carcinological risk. One such technique is *in vitro* folliculogenesis. Although the proof-of-concept has been provided in humans and oocytes at the metaphase II stage have been produced [22], their nuclear and cytoplasmic quality does not enable the use of ART techniques to produce embryos for a parental project. The other, more promising technique is the artificial ovary. This involves reconstructing an ovary from ovarian follicles isolated from the surrounding tissue and incorporating them into a biomaterial matrix, which is then transplanted into the patient.

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