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**Case Report**

# Misdiagnosed 46, XY DSD after Bone Marrow Transplantation in a Female with Acute Lymphoblastic Leukemia and Secondary Amenorrhea

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**Abstract:** Disorders of sex development (DSD) are defined as congenital conditions associated with atypical development of chromosomal, gonadal or phenotypical sex. Majority of 46XY DSD patients present clinical characteristics of primary amenorrhea. However few cases with secondary amenorrhea are reported in the literature. It was suggested that such patients might have an estrogen secretion by a tumoral lesion. In other cases, it could be a misdiagnosed 46,XY DSD following bone marrow transplantation. We report here the third case of misdiagnosed 46,XY DSD following bone marrow transplantation. Our patient is a 15-year old girl referred to our department of endocrinology for secondary amenorrhea. She had been diagnosed with lymphoblastic Leukemia at the age of 13. She received chemotherapy and total body irradiation after which she had bone marrow transplantation. The hormonal profile confirmed the primary ovarian insufficiency. Chromosomal analysis performed on peripheral blood lymphocytes showed a 46,XY karyotype consisting with a diagnosis of 46, XYDSD. However, regarding her past medical history, we complete with karyotype on skin fibroblasts that showed a normal female karyotype. Thus we conclude that our patient had a misdiagnosed 46,XYDSD, and that her secondary amenorrhea is caused by chemotherapy and radiotherapy. The fertility prognosis is considered poor in that case. Although the need for fertility preservation has to be weighed against morbidity and mortality associated with cancer, our findings highlight the importance of fertility preservation by oocyte and/or embryo cryopreservation for such patients.

**Keywords:** amenorrhea, secondary Amenorrhea, lymphoblastic Leukemia, cell transplant, primary ovarian insufficiency, Disorders of sex development.



## INTRODUCTION:

Secondary amenorrhea is defined as the cessation of regular menses for three months or the cessation of irregular menses for six months (Klein, D. A., & Poth, M. A. 2013). Most cases of secondary amenorrhea can be attributed to polycystic ovary syndrome, hypothalamic amenorrhea, hyperprolactinemia, or primary ovarian insufficiency (POI). The prevalence of POI is ~1% (Webber, L. *et al.*, 2016). The diagnosis is made when women younger than 40 years, have four or more months of amenorrhea and two serum FSH levels taken one month apart > 25 IU/l (Webber, L. *et al.*, 2016).

More than 90% of cases are idiopathic, but they can be attributed to chromosomal abnormalities, autoimmune or iatrogenic causes such us chemotherapy and radiotherapy (Webber, L. *et al.*, 2016). Disorders of sex development can also be an etiology of secondary amenorrhea. In fact a few cases of 46, XY females with secondary amenorrhea are reported in the literature (Ilter, E. *et al.*, 2008). However , it is not necessarily the right diagnosis after stem cell transplant.

## CASE REPORT:

Our patient is a 18-year old girl who presented to our clinic with secondary amenorrhea. She had been diagnosed with acute lymphoblastic leukemia (ALL) in 2012 at the age of 12 years and 11 months. Therapy began with chemotherapy with three courses according to the protocol EORTC in 2013. Then she had total body irradiation before bone marrow transplantation (BMT) because of acute lymphoblastic leukemia ALL.

Patient had menarche at 12 years and 9 months. She had regular menstruations for 5months then she developed secondary amenorrhea.

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She presented 145 cm height (-3 DS), 62kg weight, and 25 Kg/m2 BMI. Breast development was automatically since the age of 10 years and physical examination showed normal female genitalia (Tanner stage 3). She had no dysmorphic syndrome. And no family member had similar symptoms.

Laboratory examination showed an elevated follicle stimulating hormone (FSH) 84.6 mIU/mL, and luteinizing hormone (LH) 41.4 IU/mL, low estrogen (E2) 12.3pg/mL, normal prolactin (PRL) 10.6 ng/mL, normal testosterone 0.5 ng/mL and normal TSH 2.32 mIU/L. The hormonal assessment was checked and confirming the POI.

Perineal and pelvic ultrasound showed a developed and pubertal uterus and vagina, and two small ovaries with no follicular activity. Bone age was 14 years (at the age of 16).Chromosomal analysis showed 46, XY. With the doubt, we check her medical record carefully. We noticed that, she received the HLA-matched bone marrow hematopoietic stem cell from her brother. The genotype of the patient along with her whole cell line had changed after the allogeneic stem cell transplant from her brother. However, chromosomal analysis on skin fibroblasts has been done showing a normal female genotype. The patient was started on cyclical hormonal therapy, Climaston 2/10 1cp/day at the age of 16. She took 5 cm until now, with a bone age at 17 years.

## DISCUSSION:

We report here the third case of misdiagnosed 46,XY DSD following bone marrow transplantation in a female with ALL leukemia and secondary amenorrhea. Prior to Stem Cell Transplant (SCT) or bone marrow transplantation, a treatment of the recipient is obligatory. This treatment, also called "conditioning", is performed in the days preceding the transplant and has a dual purpose. It ensures adequate immunosuppression of the recipient to prevent transplant rejection in all cases, in the one hand, and aims to eradicate the underlying hematologic disease in the other hand. This treatment involves a combination of intensive chemotherapy and total body irradiation (similar to what our patient) or intensive chemotherapy alone.

One of the consequences of conditioning is infertility. In fact, the use of cyclophosphamide with total body irradiation (TBI) leads inevitably to POI (Oktem, O., & Oktay, K. 2007). Ovarian follicles constitute a principal target for chemotherapeutic agents (Huang, H., & Tian, Q. 2016). The damage is secondary to the apoptosis of primordial follicle and blood vessel damage (Oktem, O., & Oktay, K. 2007). Evidence showed that the gonadotixic effect on ovaries is variable according to the chemotherapy regimens (Huang, H., & Tian, Q. 2016). Treatment by Alkylating Agents (busulfan and cyclophosphamide), similar to what our patient has received, is associated to POI in about 100% of cases (Donnez, J. *et al.*, 2011). This type of chemotherapy has a double action. The direct one is by inducing oocyte death and the indirect one is via damage of somatic cells (Morgan, S. *et al.*, 2012). It affects the ovarian function and reserve, and led to delayed puberty or POI (Huang, H., & Tian, Q. 2016).

several risk factors for endocrine complications after SCT are reported in the literature such us underlying diseases, age at SCT, use of total body irradiation and its cumulative dose previous pre-transplant therapies, administration schedule, and post-transplant treatments (Shalet, S. M. *et al.*, 1995 ; & Brennan, B. M., & Shalet, S. M. 2002).

It is noted that pubertal or adult female' ovary function would be more affected by chemotherapy than pre-pubertal girls (Huang, H., & Tian, Q. 2016). Chemotherapy is also more toxic when administered in female with an age >30 years (Orio, F. *et al.*, 2014).

Comparing auto and allo-SCT, it was showed that allo-SCT is responsible for a more severe immunosuppressive effect of the conditioning regimens to avoid graft rejection. For this reason, allo-SCT is associated with a more severe derangement of the immune system than auto-SCT (Orio, F. *et al.*, 2014).

TBI is also responsible for a large part of post-transplant endocrinopathies (Orio, F. *et al.*, 2014), it affects ovary, hypothalamic-pituitary axis, uterus and even the urogenital tract. Loss of oocytes is dose dependent, and the dose at which 50% human oocytes are lost is < 2Gy.

Our patient has a high probability of developing POI: underlying diseases (ALL), sex, pubertal phase, Alkylating agents, TBI and allo-SCT.

Hormonal disturbances after chemotherapy can be transient. However, the hormone level of our patient confirms persistent ovarian insufficiency (Huang, H., & Tian, Q. 2016). Anti-mullerian hormone (AMH) provides a guide to ovarian reserve and is a useful marker of female reproductive function. But it has a low interest for both diagnosis and treatment. In our patient it was < 0,01ng/ml.

The particularity of this observation is the change of the karyotype to a male karyotype after CST from her full HLA matched brother. This led to a diagnostic confusion at first with disorders of sexual development patient. In fact, A few cases of 46,XY females with secondary amenorrhea are reported in the literature (Ilter, E. *et al.*, 2008). The reason for the menstrual function in these patients with 46,XY karyotype may be associated with estrogen secretion of the tumoral lesion, and investigation of gonads is always recommended.

The geneticist's opinion was to confirm the possibility of karyotype change in a gender-mismatched SCT. We complete by a karyotype on skin fibroblasts, it was 46 XX. Her karyotype is so changed to a karyotype of donor origin (her brother). Only the karyotype of hemocyte was 46 XY. However, for the other somatic cells and germ cells karyotype was 46 XX. In fact, Sex-mismatched transplantation is defined when there is a male donor and female recipient and vice versa (Erlecke, J. *et al.*, 2009). Chromosomal studies are mainly done on peripheral blood cells and bone marrow cells. In case of sex-mismatched SCT, X–Y-specific probes are systematically used in order to differentiate donor cells from recipient cells. Two similar cases were reported in literature, the first was presented with secondary amenorrhea and the second with primary amenorrhea(table1) (Huang, H., & Tian, Q. 2016 ; & Al-Jaroudi, D., & Hijazi, A. 2015).

**Table 1:** Clinical case of the other two cases of literature

| | **Case 1 (2016)** (Huang, H., & Tian, Q. (2016) | **Case 2 (2015)** (Al-Jaroudi, D., & Hijazi, A. 2015) |
|---|---|---|
| Age year | 18 | 17 |
| Motif | primary amenorrhea | secondary amenorrhea |
| Underlying disease | ALL<br>Allo-SCT : Brother, 12 years<br>CT : 12 years | ALL<br>Allo-SCT : Brother, 15 years<br>CT: 10 years + TBI |
| physical examination | height 172 cm; female genitalia A2P2S3M0 | menarche at 11 years, regular cycles 4 years |
| Laboratory examination | FSH= 73 U/ml; LH= 30 U/ml<br>E2= 23 pg/ml | |
| Perineal and pelvic ultrasound | Small uterus<br>ovaries not visualized | Small uterus and ovaries |
| Karyotype before SCT | 46XX | 46 XX |
| Karyotype after SCT | 46 XY | 46 XY |

ALL: acute lymphoblastic leukemia, SCT: Stem Cell Transplant, CT: chemotherapy, TBI: total body radiation.

No previous studies that assessed the long-term effects of Sex-mismatched after SCT on fertility were reported, and it seems that this condition could not alter gonadal function. However it is well established that chemotherapy and radiotherapy are responsible for POI.

There is a small chance of spontaneous pregnancy in case of POI, 5% to 10%. The prognosis of POI is considered poor (Huang, H., & Tian, Q. 2016). But there are several published cases that report successful pregnancy after SCT (Nakajima, Y. *et al.*, 2015).

## CONCLUSION:

We report, here, a case of an 18-years-old girl with ALL, who received chemotherapy, radiotherapy and SCT. She develops later a secondary amenorrhea and karyotype 46, XY. Her karyotype changing to that of her brother was an unexpected explication.

## DISCLOSURE:

Conflict of interest: none.

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