

# XY Chromosome in Acute Lymphocytic Leukemia Female with Secondary Amenorrhea

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## Summary

A 17-year-old girl presented to our gynecology clinic with secondary amenorrhea. She had been diagnosed with ALL at the age of 5 years; she received chemotherapy and radiotherapy over the following years. Her chromosomal analysis showed a karyotype of 46, XY.

## Abstract

The objective of this case report is to present a case of primary ovarian insufficiency in 17 year old, single girl, who had Acute Lymphocytic Leukemia (ALL) and was treated with chemo and radiotherapy, followed by bone marrow transplant from her HLA matched brother. The patient was treated at King Abdulaziz Medical City, Riyadh, Saudi Arabia. She was diagnosed with primary ovarian insufficiency, after receiving chemo and radiotherapy for ALL. In addition to counseling and emotional support, further investigations were requested which showed a 46 XY chromosomal pattern along with high FSH. A year earlier, her chromosomes were 46 XX. Hormonal replacement therapy, calcium and vitamin D were prescribed and she had withdrawal bleed. In Conclusion, this case describes a primary ovarian insufficiency in a girl post chemo and radiotherapy; it also describes a change in cell line following bone marrow transplant from her HLA matched brother.

**Keywords:** Secondary amenorrhea; Primary ovarian insufficiency; Hormonal replacement therapy; Stem cell transplant

## Introduction

The incidence of Acute Lymphocytic Leukaemia (ALL) in Saudi Arabia is 7.2% and ranks fifth after breast cancer, thyroid cancer, colorectal cancer and Non-Hodgkin's lymphoma [1].

High dose chemotherapy and radiotherapy have led to increased survival for women with acute lymphocytic leukemia (ALL) [2]. The reported 5-year survival rate for women in reproductive age group is around 40% for women with ALL [2]. However, treatment brings with it, associated morbidities, one of which is its gonadotoxic effects [2]. Therefore, fertility preservation should be discussed with patients receiving treatment for ALL [2].

Primary ovarian insufficiency is a disorder that is emotionally traumatic and bears lifelong consequences on fertility, bone and cardiovascular health [3,4], making it more challenging is its occurrence in adolescents. Previously the term premature menopause had been used and found to be incorrect; as about 50% of women have intermittent ovarian function and may ovulate and conceive after this diagnosis [3-5]. 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 in the menopausal range [3].

Causes of primary ovarian insufficiency in adolescents include chromosomal abnormalities, premutation in the FMR1 gene for fragile X, or iatrogenic from chemotherapy or radiation therapy [3]. Infiltrative, infectious processes and pelvic surgery are less common causes [3]. Autoimmune disease is another cause, as around 4% of women will have adrenal or ovarian antibodies. The etiology remains unknown in many cases [4].

Although advances in oncology treatments have improved survival of childhood cancer, this came at the expense of ovarian function, increasing the risk of ovarian insufficiency and infertility [6].

Clinicians need to be sensitive in delivering the diagnosis of primary ovarian insufficiency to their patients [6]. This diagnosis can be emotionally traumatic and emotional needs of the patient need to be addressed as should further support be available [6]. Adequate information regarding the diagnosis should be given as according to Groff et al. [7], most patients feel inadequate information decreased their sense of control [7].

We report a rare case of a female patient with ALL, who received chemotherapy, radiotherapy and stem cell transplant, and was later found to have 46 XY chromosomes. Institutional review board approval has been obtained.

## Case Report

Our patient is a 17-year old single girl who presented to our clinic with secondary amenorrhea. She had been diagnosed with Acute Lymphocytic Leukemia (ALL) in 2002 at 5 years of age.

Therapy began with hyperfractionated chemotherapy with two courses. Course A: cyclophosphamide, vincristine, doxorubicin, and dexamethasone and Course B: methotrexate and cytarabine (HCVAD). She relapsed in 2007 and 2012 and was treated with methotrexate (MTX), dexamethasone (DEXA), vincristine, L-asparagine. She then had total body radiation in 2012.

In July 2012, patient was referred to King Abdul Aziz medical city at 15 years of age with pancytopenia, she was again given hyperfractionated chemotherapy with two courses; course A: cyclophosphamide, vincristine, doxorubicin, and dexamethasone and Course B: methotrexate and cytarabine (HCVAD).

After remission, she was given busulfan/cyclophosphamide then she had Stem Cell Transplant (SCT) from her full HLA matched sibling.

Patient had menarche at 11 years, after which she had regular menstruations for 4 years before she developed secondary amenorrhea. Progesterone challenge test was done with no response. Hormonal profile showed hypergonadotropic hypogonadism, normal thyroid function test and prolactin levels. Pelvic ultrasound showed normal, but small sized uterus and ovaries. Chromosomal analysis showed 46, XY; but on review of her chromosomal analysis one-year earlier, it had been a normal female genotype. The genotype of the patient along with her whole cell line had changed after the allogeneic Stem Cell Transplant (SCT) from her HLA matched sibling. With the impression of premature ovarian insufficiency as her primary diagnosis, the patient was started on cyclical hormonal therapy, estradiol valerate 2 mg, norgestrel 500 mcg (progluton<sup>®</sup>, Bayer Health, Germany) along with calcium and vitamin D for 6 months. On follow up after 4 months, the patient had withdrawal bleeds and she was advised to continue on the same treatment.

## Discussion

Conditioning prior to Stem Cell Transplant (SCT) particularly with cyclophosphamide and total body irradiation will inevitably lead to primary ovarian insufficiency and infertility [8]. The risk of primary ovarian insufficiency when patients receive busulfan and cyclophosphamide is about 100%, similar to what our patient has received [8].

We report this case as this patient's karyotype changed to a male karyotype following Stem Cell Transplant (SCT) from her full HLA matched sibling. This led to a diagnostic confusion at first, and was later clarified after reviewing her karyotype one year earlier. The genetist was consulted and concurred with the possibility of the chromosomal change in a gender-mismatched stem cell transplantation.

No similar cases were reported in literature, although numerous cases were reported on primary ovarian insufficiency in adolescents, and successful pregnancy thereafter [5].

Reports on sex-mismatched transplantation and its long-term effects on health have been described [9]. Sex-mismatched transplantation is defined when there is a male donor and female recipient and vice versa [9]. In these instances, it is possible to classify donor and acceptor cells in the bone marrow or blood

cell system. Complete chimerism is defined when there are 100 percent donor cells; however, mixed chimerism is defined when there is a mixture of both donor and acceptor cells [9]. In order to exclude minimal residual disease, the chimerism analysis is done on these sex-mismatched transplants. This will further assess future treatment plans like Donor Lymphocyte Infusion (DLI) [9].

Automated detection of residual cells after sex-mismatched stem-cell transplantation has been reported in literature [9]. Its main purpose is to determine the relapse or rejection ascertain various responses to different treatment modalities [9].

In order to differentiate between donor and recipient cells, cytogenetic analysis is usually performed and when the donor and recipient are sex matched, characteristic polymorphic regions or satellites are used to distinguish the donor or recipient origin of dividing cells. In case of leukemia, chromosomal rearrangement with loss of genetic information such as monosomies or deletions happens and thus cytogenetic analysis becomes an important aspect for analyzing chimerism [9]. These chromosomal studies are mainly done on peripheral blood cells and bone marrow cells of the metaphase stage. X-Y-specific probes are used for the cases of sex-mismatched Hematopoietic Stem Cell Transplantation (HSCT) in order to differentiate donor cells from recipient cells [10]. The main purpose is to predict negative events like disease relapse, graft rejection and graft-versus-host disease, and thus, chimerism analysis is generally used in order to monitor the outcomes post HSCT [10].

Khan *et al.* [11] has reported loss of the Y-chromosome and duplication of the X-chromosome in the host cells. However, the report was for a 12-year-old male with pre-B-cell acute lymphoblastic leukemia who underwent sex-mismatched allogeneic bone marrow transplantation. Complete donor chimerism was detected after the Y-chromosome-specific quantitative polymerase chain reaction and sex chromosome-specific interphase Fluorescence In Situ Hybridization (i-FISH) was done [11]. They concluded that after allo-BMT chromosomal changes can lead to difficulties in chimerism analysis [11].

In another report, the Y-chromosome-based PCR techniques has been suggested to be the most efficient means of detecting minimal residual male cells in male host when there is gender-mismatched HCT hematopoietic stem cell transplantation [12]. This is not true when the recipient is a female, since the detection rate is much lower [12].

These studies highlighted the importance of these tests for the long-term follow-up period of HCT patients. Our case was different since the findings were incidental upon investigating other causes of amenorrhea. The aim was not to detect residual male cells in order to assess the need for further future treatment.

It has to be noted, that chromosomal pattern can change after allogeneic stem cell transplant. Additionally, fertility preservation options should be discussed with patients prior to chemotherapy and radiotherapy.

Nonetheless, this patient was offered counseling and hormonal therapy after she was referred to the clinic. The

aim of hormonal therapy in adolescents with primary ovarian insufficiency includes the relief of hypoestrogenic symptoms in addition to bone support, cardiovascular, and sexual health [13]. Adolescents may need higher doses of estrogen in comparison to menopausal women to ensure adequate replacement and optimal bone health [13].

There are several case reports that describe successful pregnancy following stem cell transplant (SCT) [14]. Nakajima et al, describe a successful pregnancy after *In vitro* Fertilization (IVF) and a full term delivery in a 42-year-old woman with Acute Myeloid Leukemia (AML) who became pregnant 2 years and 2 months after allogeneic Stem Cell Transplant (SCT) [14].

Multidisciplinary treatment approach should be the aim when treating patients with cancer. Oncologists, infertility specialists, and psychologists should work together to provide the patients with the best possible care in terms of survival, satisfaction, counseling and fertility potential.

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