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Case Report

Live birth after intracytoplasmic sperm injection using self-sperm in a male with 46, XX karyotype resulting from complete chimerism following bone marrow transplant from a human leukocyte antigen matched sibling

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ABSTRACT

Gonadal dysfunction and definitive infertility are common long-term non-malignant effects after bone marrow transplantation (BMT), particularly when chemotherapy is part of the conditioning regimen. We report a case of a 44-year-old male with a history of thalassemia major who underwent allogeneic bone marrow transplant at the age of 18 years from his human leukocyte antigen (HLA)-matched sister. He subsequently developed complete hematopoietic chimerism with a 46, XX karyotype and testicular failure secondary to chemotherapy. The patient presented with primary infertility and azoospermia. Medical management was continued for 10 months using gonadotrophins to stimulate spermatogenesis following which ICSI was done for the couple using self-semen to achieve live birth.

Keywords: Azoospermia, Complete chimerism, Bone marrow transplantation, ICSI, Thalassemia major

INTRODUCTION

Currently, Allogeneic hematopoietic stem cell transplantation (HCT) is an efficient curative approach for different hematologic diseases, However, despite its therapeutic success, HCT is frequently associated with long-term complications, one of the most significant being gonadal failure and impaired fertility potential, particularly among young survivors.[1] Gonadal toxicity of the chemotherapy used as part of the conditioning regimen plays a central role in post transplantation infertility by adversely affecting the germinal epithelium, possibly leading to azoospermia or oligozoospermia.[2-4] Young HCT survivors frequently report infertility concerns as a late effect of HCT and loss of fertility can have a negative impact on their reproductive and overall quality of life.[5-7] Nevertheless, there have been rare instances of successful fatherhood following transplantation, even in patients with severely impaired sperm parameters, often through the use of assisted reproductive technologies.[8]

Assisted reproductive technology has improved to the point of achieving pregnancies for severely infertile couples; in particular, intracytoplasmic sperm injection (ICSI). Here we report a case of a successful live birth using self-semen in an infertile male with complete chimerism (karyotype 46, XX) and testicular failure.

CASE REPORT

In February 2023, a 32-year-old woman and her 44-years -old husband were referred to our clinic. The couple had been trying to achieve a pregnancy for 12 years. The female partner was having irregular cycles suggestive of

oligo/anovulation and exhibits polycystic ovarian morphology but no other severe endocrine abnormalities. Woman's physical and gynaecological examinations were within normal limits.

Male partner history: History of thalassemia major since the age of 3 months old and had received multiple blood transfusion along with chelation therapy with Desferroxamine. He had undergone splenectomy at the age of 12 years. Post-transfusion he contracted Hepatitis C. At the age of 18 years, He had undergone bone marrow transplantation (BMT) from his human leukocyte antigen (HLA) matched sister with conditioning chemotherapy (busulfan with cyclophosphamide). The transplantation was preceded by a myeloablative conditioning regimen with cyclophosphamide (160 mg/kg) and busulfan (14 mg/kg). The GVHD prophylaxis was carried out with cyclosporin A (CSA) and short-course methotrexate (MTX). CSA was started at the dose of 6.75 mg twice daily by continuous intravenous infusion from day-4. Dosage was adjusted accordingly to the levels. He did not develop graft versus host reaction at that time. No other post-transplant complication was recorded. He was diagnosed with hypothyroidism and was on replacement therapy with thyroxine 25 mcg. He was also recently diagnosed with diabetes mellitus and was on oral hypoglycaemic agents (Linagliptin with Metformin) and later presented with primary infertility. He reported no family history of infertility.

At physical examination, he had normal secondary sexual features (androgenicity), normal penile length and structure and no gynaecomastia. Both testes were atrophic, B/L vas palpable, no clinical varicocele. This man reported normal libido and normal erectile function. Semen analysis was done outside on multiple occasions suggestive of azoospermia. Initial semen analysis was tried at our centre in 2023 on two separate occasions (one week apart) but it could not be done as he was having very low volume ejaculate (only a drop or two and same examined under microscope did not show any spermatozoa). His endocrine parameters were as follows, FSH 5.42 miu/ml, LH 3.06 miu/ml, Testosterone 0.2 ng/ml, estradiol 5 pg/ml, TSH 3.4miu/ml. Karyotyping (peripheral blood): 46, XX (consistent with donor cells) (Figure 1). Y chromosome microdeletion testing was done, which showed all regions of y chromosome were absent (Table 1) (no Y chromosome in karyotype). Scrotal doppler was done in same visit suggestive of B/L shrunken testis, right testis measures 1.5×0.9×1.2 cm, volume 0.95 cc, left testis measures 1.7×1.3×0.8 cm, volume 1 cc. His low testosterone levels (in female range), reduced testicular volume, and severely impaired spermatogenesis suggest non-obstructive azoospermia possibly due to gonadotoxic treatment. His blood group was O positive. (Prior to the bone marrow transplant, his blood group was A positive and it changed from A positive to O positive after receiving a bone marrow transplant from his O negative sister).

On the basis of these results, the couple were counselled in detail. After explaining the poor prognosis, he was advised to start medical treatment using gonadotrophins and to have follow-up every 2-3 monthly interval to assess the effectiveness of medical treatment. The primary intention of the medical treatment was to increase the serum testosterone level. In the beginning itself he was counselled about the empiric nature of therapy. Medical management was started in February 2023 with Inj. Hp HMG 150 IU two times a week and inj. Hcg 5000 IU two times a week and was continued and planned for a review in July 2023. His follow-up endocrinological evaluation in July 2023 was as follows: FSH 7.01 miu/ml, Testosterone 6.55 ng/ml (significantly increased from the last seen value in Feb 2023), semen analysis in July was showing a volume of 0.5 ml and few immotile spermatozoa in the centrifuged sample but with poor morphology. The same gonadotrophin was continued along with a combined antioxidant and vitamin C supplementation and he was planned for a review consultation in Dec 2023. His endocrinological evaluation in Dec 2023 was as follows: FSH 9.10 miu/ml, Testosterone 5 ng/ml. Semen analysis in Dec 2023 was having a volume of 0.5 ml, count of less than 1 million/ ml, semen was having few non progressive motile sperms and few morphologically normal sperms were also observed in the sample. He was now counselled for ICSI and advised to freeze 3 semen samples prior to the female partner's ovarian stimulation. Three semen samples were frozen in February 2024.

Controlled ovarian stimulation was started for the female partner in Feb 2024 with flexible antagonist protocol. Her BMI was 21 Kg/m2, AMH-5.65 ng/ml and AFC was 41. Ovarian stimulation was started with recombinant FSH-200 IU and Hp HMG 75 IU. GnRH antagonist-cetrorelix 0.25 mg/day was started from fifth day of stimulation and same gonadotrophin dose was continued. GnRH agonist trigger (Decapeptyle 0.4 mg) was administered for final oocyte maturation after 9 days of ovarian stimulation. Vaginal ultrasound-guided follicle aspiration took place 36 h after the final trigger injection.

We retrieved 31 mature (M II) oocytes, Ejaculate semen was used for ICSI (both frozen and fresh ejaculate was used). 22 zygotes were formed on day 1. A total of 6 embryos were formed. Four day-3 grade A (1X12 cell, 1X9 cell, 1X10 cell,1X8 cell), one day-3 grade B (1X8 cell) and one day-5 (1X2BC) were formed. All the embryos were cryopreserved and was transferred in the subsequent cycle.

1st Frozen embryo transfer was done in April 2024.The endometrium was prepared using downregulated hormone replacement therapy (HRT) cycle. After adequate endometrium preparation, two day-3 grade A embryos were transferred. Luteal support was continued for 12 days after embryo transfer. The first beta HCG after 12 days was 14.18 miu/ml. Subsequent beta HCG on 14th day was 11 miu/ml. Luteal support was stopped after the second beta HCG. Patient underwent 2nd frozen embryo transfer

cycle in June 2024. Endometrium was prepared using down regulated HRT protocol. After adequate estrogen exposure and after adequate endometrial thickness, 3 day-3 (2x grade A, 1x grade B) embryos were transferred. Luteal support was continued. The quantitative serum HCG level 12 days after embryo transfer was 111miu/ml and with a progressive rise in beta HCG which was repeated 48hrs later. At 7 weeks of gestation, a singleton pregnancy and a fetal heartbeat were confirmed by transvaginal ultrasound. Luteal phase support was continued till 10 weeks of gestation. In 2025, at 39 weeks of gestation, the patient delivered a healthy female baby of 3000 g, 46, XX, blood group of A positive consistent with father's original ABO and Rh typing (i.e. A positive). Mother's blood group was O positive.

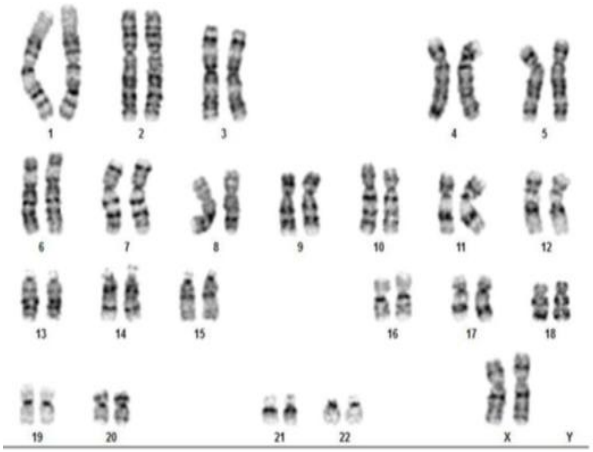

Figure 1: Chromosome karyotype analysis in peripheral blood.

Table 1: Y chromosome microdeletion report in peripheral blood sample.

STS	Region	Fragment size (bp)	Results
SY14	SRY	472- DNA control	Absent
ZFX/Y	ZFX/ZFY	495- DNA control	Absent
sY84	AZFa	327	Absent
sY86	AZFa	306	Absent
sY82	AZFa	264	Absent
sY746	AZFa	216	Absent
sY143	AZFb	331	Absent
sY134	AZFb	303	Absent
sY127	AZFb	274	Absent
sY128	AZFb	228	Absent
sY121	AZFb	190	Absent
sY130	AZFb	173	Absent
sY254	AZFc	380	Absent
sY160	AZFc	236	Absent
sY145	AZFc	143	Absent
sY255	AZFc	126	Absent

DISCUSSION

Chimerism refers to the presence of two genetically distinct cell lines in an individual. Artificial chimerism can arise from transfused blood stem cells, either by intrauterine transfusion or by allogenic bone marrow transplantation (BMT), as well as other organ transplantations.[9] In sex-mismatched hematopoietic stem cell transplantation (HSCT), complete donor-derived hematopoietic chimerism is a well-recognized phenomenon and is commonly demonstrated by peripheral blood karyotyping or chimerism analysis using short tandem repeat (STR) markers.[10]

In this case, complete hematopoietic chimerism with a donor-derived 46, XX karyotype was confirmed in a phenotypic male following female-to-male allogeneic HSCT. Although the peripheral blood karyotype reflected complete donor engraftment, the patient's genetic sex and gonadal tissue remained unchanged, because Genetic sex is determined when the ovum is fertilized with sperm containing X or Y chromosomes.[9] In XY individuals, the SRY gene on the Y chromosome initiates testicular development and subsequent male sexual differentiation. Therefore, in patients who undergo sex-mismatched BMT/HSCT, transplantation does not change their pre-existing genetic or physiological sex. The donor-derived sex chromosomes detected in peripheral blood reflect hematopoietic chimerism, rather than a change in the recipient's constitutional or gonadal sex. This distinction is important to avoid misdiagnosis of disorders of sex development in patients with a history of sex-mismatched transplantation.[11]

This case highlights a rare cause of male infertility: complete hematopoietic chimerism with a female (46, XX) karyotype following female-to-male allogeneic hematopoietic stem cell transplantation (HSCT). The patient's azoospermia and gonadal insufficiency were most likely secondary to gonadotoxic conditioning therapy, particularly exposure to alkylating agents such as busulfan and cyclophosphamide, which are well-established causes of impaired spermatogenesis and, in some patients, Leydig cell dysfunction after HSCT.[12,13] Previous studies have shown that TBI is a strong independent predictor of persistent azoospermia after HSCT.[12] The patient developed azoospermia and gonadal insufficiency due to gonadotoxic conditioning therapy. In the initial assessment, the severely low serum testosterone could be a cause the persistent very low volume ejaculate. Increased serum testosterone after the medical therapy with gonadotrophin helped to achieve a semen volume of 0.5 ml, that could be examined for the presence of sperm. It emphasizes the need of checking semen on repeated occasions and the role of gonadotrophin in increasing the serum testosterone level and a potential role of gonadotrophin in augmenting the sperm production.

A similar case was reported by Teng et al in 2025 in a 22-year-old male with azoospermia in whom complete

chimerism was identified, but as the patient was not seeking fertility treatment, no reproductive intervention was performed.[10] In contrast, in present case a live birth was achieved following fertility treatment in a patient with complete chimerism after opposite-sex allogeneic bone marrow transplantation.

CONCLUSION

Complete opposite-sex hematopoietic chimerism following allogeneic HSCT does not imply a 46, XX germline and does not preclude biological paternity. This case demonstrates that post-HSCT azoospermia may not represent irreversible infertility, and residual spermatogenesis should be actively sought through repeated semen analysis and, when appropriate, surgical sperm retrieval.

Gonadotrophin therapy may help correct reversible endocrine dysfunction, although its role in primary chemotherapy-induced testicular failure remains uncertain. Fertility preservation and long-term reproductive assessment should therefore remain integral to the care of HSCT survivors.

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