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Spontaneous conception in a 40-year-old woman after allogeneic stem cell transplant with active graft-versus-host disease: A case report

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ABSTRACT

This article presents a case of spontaneous conception and live birth in a 40-year-old woman who had undergone gonadotoxic chemotherapy and allogenic stem cell transplant for relapsed acute myelogenous leukemia complicated by treatment-refractory graft-versus-host disease. The patient's follicle stimulating hormone level was 44.4 mIU/mL at age 38 and then decreased to 4.1 mIU/mL at age 41, suggesting ovarian recovery. Her graft-versus-host disease subjectively improved during pregnancy. She ultimately delivered a healthy neonate. This case demonstrates the potential for ovarian recovery after stem allogenic cell transplant in a patient of advanced reproductive age and provides insight into the limited knowledge about graft-versus-host disease in pregnancy. As survival after stem cell transplant continues to improve, understanding the downstream consequences of the treatment, including for fertility and pregnancy, is of growing importance.

1. Introduction

Allogeneic hematopoietic stem cell transplantation (SCT) is a mainstay of treatment for acute myeloid leukemia (AML), and its use is growing globally [1]. SCT involves wiping out abnormal hematopoietic cells using chemotherapy and/or radiation and then transplanting donor hematopoietic stem cells to restore the bone marrow [1]. Most pre-transplant conditioning protocols involve gonadotoxic treatments such as alkylating agents, radiation, or both [2]. These treatments often result in premature ovarian insufficiency (POI) [1]. Su et al. observed that 83% of women suffered from secondary amenorrhea and 73% met criteria for POI after SCT [1]. Similarly, Nathalie et al. reported POI in 74% of women who underwent SCT before age 35 [3]. Sanders et al. similarly found that only 16% of postpubertal females regained normal ovarian function after SCT [4]. The probability of POI after SCT is significantly associated with advancing age at the time of SCT [1,5,6]. Pregnancy rates, including both spontaneous conception and conception using assisted reproductive technology, in the post-SCT population are reported to be low (0.6% - 13%) [3,4,7]. Pregnancies after SCT have also been found to be at increased risk of complications [4,7]. Additionally, information regarding conception and pregnancy in the setting of graft-versus-host disease (GVHD) is scarce; no large studies in this population have been published [8].

We describe a case of spontaneous conception in a woman who had undergone SCT at advanced reproductive age with resulting GVHD and ovarian dysfunction. While other cases of pregnancy after SCT have been reported, this is apparently the first specifically highlighting spontaneous conception after SCT for AML relapse in a woman of advanced reproductive age with active chronic GVHD.

2. Case Presentation

A 41-year-old woman with a history of AML who had previously undergone chemotherapy and SCT presented to the gynecology department as part of a multidisciplinary protocol for refractory chronic GVHD. She provided informed consent for the publication of this report. Prior to her cancer diagnosis, the patient's medical history was notable for chronic hypertension and anxiety. Her obstetric history included one

Abbreviations: AMH, anti-müllerian hormone; FLAG-GO, fludarabine, cytarabine, granulocyte colony-stimulating factor, gemtuzumab ozogamicin; HLA, human leukocyte antigen; FSH, follicle stimulating hormone; GVHD, graft-versus-host disease; POI, premature ovarian insufficiency; SCT, allogeneic stem cell transplant; AML, acute myeloid/myelogenous leukemia.

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first-trimester miscarriage followed by two full-term cesarean deliveries. She achieved menarche at age 14 and had regular menstrual cycles.

She was initially diagnosed with AML with inversion of chromosome 16 at an outside facility at age 36 after several months of fatigue and respiratory symptoms. She underwent induction chemotherapy with cytarabine and idarubicin. Follow-up bone marrow biopsy demonstrated clinical remission, after which she received consolidation chemotherapy with high-dose cytarabine. Bone marrow biopsy approximately 1.5 years later revealed relapse of disease, for which she underwent FLAG-GO chemotherapy (fludarabine, cytarabine, granulocyte colony-stimulating factor, gemtuzumab ozogamicin). After this treatment she achieved morphologic clinical remission but remained positive for the CBFB-MYH11 fusion transcript; as such, at age 38 she received fludarabine/melphalan 140 mg/m2 conditioning and underwent a sex-matched unrelated donor peripheral blood stem cell transplant of 2.87 × 10^6 CD34+ cells/kg. The donor and the patient were also matched in regards to human leukocyte antigen compatibility (HLA 10/10), blood type, cytomegalovirus status, and toxoplasmosis exposure. Post-transplant bone marrow biopsy three months after transplant showed no evidence of disease. The patient took methotrexate and tacrolimus for GVHD prophylaxis; however, she was diagnosed with GVHD affecting the eyes, skin, oral mucosa and liver two months after transplant. Despite various treatments such as steroids, mycophenolate, ruxolitinib, belumosudil, phototherapy, and intravenous immunoglobulins, her GVHD remained refractory.

Her menstrual cycles after SCT became irregular and heavier; she was initially amenorrheic for the first 10–11 months after transplant and then experienced irregular cycles, varying from oligomenorrhea to polymenorrhea. Endometrial tissue evaluation was benign. Laboratory testing six months after transplant at age 38 revealed a follicle stimulating hormone (FSH) level in the menopausal range at 44.4 mIU/mL and anti-müllerian hormone (AMH) <0.015 ng/mL. Given these findings, she was told by the outside facility that she was infertile and did not require contraception. She was not on hormone replacement therapy. Approximately 1.5 years later, at age 40, she was shocked to discover she had unintentionally conceived. In addition to her ongoing GVHD, her pregnancy was also complicated by gestational diabetes A1, severe fetal growth restriction, advanced maternal age, and superimposed preeclampsia with severe features. Noninvasive prenatal testing was low risk for aneuploidy. She had been taking belumosudil and mycophenolate for her GVHD, which she discontinued upon diagnosis of pregnancy. Her GVHD remained stable throughout pregnancy on prednisone 10 mg daily and oxycodone 10 mg as needed. The superimposed preeclampsia with severe features was diagnosed at 36 weeks of gestation, at which point she underwent magnesium therapy and cesarean section. She delivered a baby boy weighing 1.73 kg (<1st percentile), small for gestational age but otherwise healthy. The remainder of her postpartum course was uncomplicated, and the neonate was discharged home 11 days after delivery.

After pregnancy, the patient's GVHD affecting her lower extremities worsened and proved treatment refractory despite restarting belumosudil, mycophenolate, and phototherapy, prompting referral to a national research facility. Three years after transplant, at age 41, repeat labs demonstrated FSH 4.1 mIU/mL and estradiol <10 pg/mL. The patient continued to undergo treatment at a research center as part of a multidisciplinary protocol for refractory GVHD.

3. Discussion

This report describes a novel case of a patient who underwent SCT for relapsed AML, was of advanced reproductive age at the time of treatment and conception, and had active chronic GVHD and who despite all odds conceived spontaneously to deliver a healthy neonate. The use of SCT has been increasing for decades in parallel with improved survival after transplant [1,5]. With more women of reproductive age living longer after SCT, understanding the downstream consequences of the treatment, including for fertility and pregnancy, is increasingly important.

The chance of a patient conceiving spontaneously at age 40 is approximately 5% per menstrual cycle. Additionally, the risk of chromosomal abnormalities in the fetus also increases with maternal age. At age 40, the present patient's pregnancy carried a 1 in 40 risk for chromosomal abnormalities; however, all screening was negative and the baby is now a healthy toddler [9].

Furthermore, one of the most important risk factors for ovarian failure and infertility after SCT is advanced age at the time of treatment [1,2,5,6]. Su et al. reported that 100% of women aged 21–40 at the time of SCT suffered from POI, compared with 62.5% of those aged 11–20 ($p < 0.01$) [1]. Similarly, Loren et al. noted those who underwent SCT before age 20 were more likely to have preserved fertility [5]. Schechter et al. also described improved ovarian recovery in those who underwent SCT before age 25 and observed no pregnancies in those treated after age 29 [2]. The patient in this report underwent SCT at age 37, and so conception at age 40 was even more improbable.

Chronic GVHD affects 40–50% of SCT recipients; however, the literature on GVHD in pregnancy is limited [10], with no sizable studies in this population. The few published case reports describe younger patients with well-controlled GVHD after SCT for non-malignant disorders, some of whom conceived using oocytes cryopreserved prior to treatment [8,11]. The current patient's case is unique because she had active GVHD, underwent transplant for a malignant condition, was of advanced reproductive age, and conceived spontaneously. Her GVHD remained stable throughout pregnancy on just prednisone and oxycodone and then worsened after delivery, potentially supporting murine model findings that pregnancy-specific glycoprotein 1 may serve a protective role against GVHD [12].

Prior studies reported an increased risk of complications such as preterm delivery, low birth weight, and cesarean delivery in pregnancies following SCT [4,7]. This patient's pregnancy was complicated by all three of these factors, supporting these prior findings. It is worth noting, however, that her history of two prior cesarean sections made cesarean delivery the recommended mode of delivery regardless of her SCT.

This case provides multiple learning points. First, it demonstrates that the post-transplant ovary may be more resilient than previously understood; as such, providers must properly counsel patients about the potential of recovered fertility and the need for contraception if pregnancy is not desired. Second, those who do wish to conceive after SCT should be advised about the complications associated with pregnancy after transplant, such as preterm delivery and low birth weight, which this case reinforces. Early involvement of maternal fetal medicine is crucial. Lastly, this case demonstrates that active GVHD does not appear to be a contraindication to pregnancy. In fact, this patient's improved GVHD symptoms during pregnancy combined with murine study findings suggest that pregnancy-associated proteins may contribute to novel treatments against GVHD.

A strength of this case report is that it calls into question what has been previously accepted about the low likelihood of ovarian recovery after undergoing gonadotoxic treatment at an advanced age. Another strength is that it garners attention to pregnancy with GVHD, which is not well studied. The lack of prior investigation on GVHD in pregnancy also limits the generalizability of this patient's experience.

4. Conclusion

This case highlights not only that ovarian recovery and spontaneous conception are possible after SCT at an advanced age, but also that pregnancy with active chronic GVHD is feasible. SCT recipients must be counseled appropriately to understand their reproductive potential and risks. Optimal care of these patients requires a multidisciplinary team. Prospective research on reproductive outcomes after SCT and GVHD in pregnancy is warranted as this patient population continues to grow.

Contributors

Lauren Barrison contributed to patient care, conception of the case report, acquiring and interpreting the data, drafting the manuscript, undertaking the literature review and revising the article critically for important intellectual content.

Selena Park contributed to patient care, conception of the case report, acquiring and interpreting the data and revising the article critically for important intellectual content.

Alan Decherney contributed to patient care, conception of the case report and revising the article critically for important intellectual content.

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Patient consent

Obtained.

Provenance and peer review

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Conflict of interest statement

The authors declare that they have no conflict of interest regarding the publication of this case report.

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