HHS Public Access

Author manuscript

Endocr Pract. Author manuscript; available in PMC 2016 January 04.

Published in final edited form as:

Endocr Pract. 2014 September ; 20(9): e157–e161. doi:10.4158/EP13474.CR.

SUCCESSFUL FERTILITY RESTORATION AFTER ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION

Helen Gharwan, MD, DrSc[1], **Nicola M. Neary, BM, BCh, PhD**[2], **Mary Link, RN**[3], **Matthew M. Hsieh, MD**[3], **Courtney D. Fitzhugh, MD**[3], **Richard J. Sherins, MD**[4], and **John F. Tisdale, MD**[3,4]

[1]National Cancer Institute, Medical Oncology Branch, Bethesda, Maryland [2]Department of Endocrinology, St. George's Hospital, Blackshaw Road, London, United Kingdom [3]National Heart, Lung, and Blood Institute, Molecular and Clinical Hematology Branch, Bethesda, Maryland [4]Columbia Fertility Associates, Washington, DC

Abstract

Objective—Myeloablative conditioning regimens given prior to hematopoietic stem cell transplantation (HSCT) frequently cause permanent sterility in men. In patients with sickle cell disease (SCD) we use a nonmyeloablative regimen with sirolimus, alemtuzumab, and low-dose total-body irradiation (300 centigrays) with gonadal shielding preceding allogeneic HSCT. We report here the restoration of azoospermia in a patient with SCD after allogeneic HSCT. We discuss the impact of our patient's underlying chronic medical conditions and the therapies he had received (frequent blood transfusions, iron chelating drugs, ribavirin, hydroxyurea, opioids), as well as the impact of the nonmyeloablative conditioning regimen on male gonadal function, and we review the literature on this topic.

Methods—We determined the patient's reproductive hormonal values and his semen parameters before, during, and after HSCT and infertility treatment. In addition, we routinely measured his serum laboratory parameters pertinent to SCD and infertility, such as iron and ferritin levels. A karyotype analysis was performed to assess the potential presence of Klinefelter syndrome. Finally, imaging studies of the patient's brain and testes were done to rule out further underlying pathology.

Results—A 42-year-old man with SCD, transfusional iron overload, and hepatitis C underwent a nonmyeloablative allogeneic HSCT. One year later he desired to father a child but was found to be azoospermic in the context of hypogonadotropic hypogonadism. Restoration of fertility was attempted with human chorionic gonadotropin (2,000 IU) plus human menopausal gonadotropin (75 IU follicle-stimulating hormone) injected subcutaneously 3 times weekly. Within 6 months of treatment, the patient's serum calculated free testosterone value normalized, and his sperm count and sperm motility improved. After 10 months, he successfully initiated a pregnancy through

Address correspondence to Dr. Helen Gharwan, National Cancer Institute, Medical Oncology Branch, Bethesda, MD 20892. helen.gharwan@nih.gov.

DISCLOSURE

The authors have no multiplicity of interest to disclose.

intercourse. The pregnancy was uncomplicated, and a healthy daughter was delivered naturally at term.

Conclusion—Despite exposure to several gonadotoxins, transfusional iron overload and nonmyeloablative conditioning with radiation causing severe testicular atrophy suggesting extensive damage to seminiferous tubules and possibly Leydig cells, gonadotropins were efficacious in restoring our patient's reproductive capability.

INTRODUCTION

Infertility in males with sickle cell disease (SCD) can be multifactorial in etiology, related either to the disease itself (priapism [1], hypothalamic-pituitary-gonadal dysfunction [2], testicular ischemia/infarction secondary to erythrocyte sickling [1], testicular dysfunction due to systemic oxygen deficit [3], and/or zinc deficiency [4]) or to the therapeutic management (repeated erythrocyte transfusions that may result in iron deposition in gonadotrophic cells [5] and/or long-term use of iron chelators [6], hydroxyurea [7], and opioids [8]). Hematopoietic stem cell transplantation (HSCT), the only curative treatment for SCD, with success rates up to 95%, can eradicate a patient's need for blood or exchange transfusions while allowing for therapeutic phlebotomies. However, HSCT can cause various types of endocrine dysfunction, including transient or even persistent reproductive failure (9).

Here, we report the case of a male patient with SCD who, after HSCT, was found to be azoospermic due to hypogonadotropic hypogonadism but whose reproductive function was successfully restored, such that he naturally fathered a child despite previous exposure to several gonadotoxic agents.

CASE REPORT

A 42-year-old man with homozygous SCD (Hb SS, defined as homozygosity for the mutation that carries hemoglobin S) diagnosed at 2 years of age presented after allogeneic peripheral blood SCT from a sibling donor for fertility evaluation. He had normal onset of puberty at age 13 years, unintentionally impregnated his partner at age 20, experienced decreased testicular size and some decrease in libido at age 22 and transfusion-related hemosiderosis by age 25 (due to an estimated 250 units of erythrocyte transfusions up to that time), prompting start of iron chelation with desferoxamine (and subsequently deferasirox) and regular phlebotomies. At 26 years of age, he began exhibiting hydroxyurea. At age 28, he noted a further decrease in libido. At 30 years of age, he was diagnosed with hepatitis C (genotype 2A), with biopsy-confirmed hepatic hemosiderosis, moderate inflammation, and fibrosis. At age 33, he developed gynecomastia, which was corrected with bilateral reduction mammoplasties. By 39 years of age, he had lost all sexual drive.

At 40 years of age, the patient presented for consideration of HSCT. He first received a 9-month course of interferon and ribavirin and became seronegative for hepatitis C. At 41 years of age, he underwent uncomplicated HSCT following nonmyeloablative conditioning comprised of alemtuzumab followed by 1 dose of total-body irradiation (TBI) with 300 centigrays (cGy) using testicular shielding (10). Immunosuppression was achieved with

sirolimus (11). One year after HSCT, despite continued lack of libido and persistent fatigue, the patient desired to father a child with his 39-year-old partner, who had neither SCD nor carried the sickle cell trait. On physical examination, he had normal virilization and no residual gynecomastia. Both testes were soft and atrophic, with decreased orchidometric volumes (5 mL bilaterally [normal adult, 17 to 32 mL]). The prostate gland was not palpable. Laboratory investigations confirmed low serum testosterone along with inappropriately low gonadotropin levels (fasting 9 am total testosterone, 262 [range, 300 to 1,000 ng/dL]; sex hormone–binding globulin [SHBG] markedly elevated at 128 nmol/L [normal, 13 to 71 nmol/L]; calculated free testosterone [cFT], 1.9 [normal, 7.4 to 22.6 ng/dL]; luteinizing hormone [LH], 5.4 [normal, 1 to 9 U/L]; follicle-stimulating hormone [FSH] 4.2 [normal, 1 to 9 U/L]). A thyroid panel and a 250-μg short synacthen (adrenocorticotropic hormone) adrenal stimulation test were normal. The insulin-like growth factor 1 level was low, at 82 ng/mL (normal, 101 to 267 ng/mL).

The hypogonadotropic hypogonadism and likely growth hormone deficiency were attributed to hemochromatosis secondary to numerous blood transfusions; the patient's serum ferritin level before HSCT had been 5,121 μg/L (normal, 18 to 370 μg/L), and although considerably decreased with intermittent iron chelation and regular phlebotomies, his serum ferritin level was still elevated, at 1,452 μg/L 1 year after HSCT. A T2-weighted pituitary magnetic resonance imaging scan was unremarkable, with a homogenous bright signal and no evidence of iron deposition, although this does not rule out pituitary hemosiderosis (12). The exceptionally high SHBG level was attributed to hepatic hemosiderosis and hepatitis C, contributing to the very low cFT level.

Although the laboratory tests were consistent with central hypogonadism, the examination findings of such small testes suggested possible additional concomitant primary hypogonadism. Semen analysis revealed azoospermia; the patient's ejaculate volume was 0.9 mL (normal, ≥1.5 mL per World Health Organization 2010 criteria). The patient's karyotype was 46,XY, excluding Klinefelter syndrome.

To restore fertility, the patient was begun on human chorionic gonadotropin (hCG) (2,000 IU) plus human menopausal gonadotropin (hMG; 75 IU FSH), self-administered subcutaneously 3 times weekly. Within 4 months of treatment, his libido improved and he became sexually active. His cFT level rose to 9.3 ng/dL and his SHBG level decreased to 94 nmol/L (Table 1). The patient's testicular volume increased to 7 mL and his semen volume to 1.9 mL, with the appearance of motile sperm (51%) at 0.76×10^6 in a single ejaculate (Table 2).

After 10 months of gonadotropin therapy, the patient's partner, who did not carry the sickle cell gene, conceived naturally. The pregnancy was uncomplicated, and a healthy daughter was delivered at term. Hemoglobin electrophoresis revealed that the newborn carried the sickle cell trait.

DISCUSSION

The prevalence of hypogonadism in patients with SCD is approximately 25% and includes secondary (hypothalamic- pituitary) and primary (testicular) hypogonadism (2). Iron overload due to chronic blood transfusion therapy is a major contributor to both these forms of hypogonadism. Excess iron may deposit in multiple organs, including the liver, the pancreas, the pituitary gland, and the gonads. Additionally, our patient suffered from frequent vasoocclusive crises prior to his HSCT, which were treated with intermittent opioids and regular hydroxyurea.

Opioids suppress the hypothalamic-pituitary axes, particularly the gonadal axis (13), and may have contributed to our patient's secondary hypogonadism. Hydroxyurea (HU) is a nonalkylating antineoplastic agent, which inhibits ribonucleotide reductase during the cell cycle's synthesis phase, thereby inhibiting DNA synthesis. The scant data on its effect on human spermatogenesis and male fertility are consistent with results seen in rodents, where HU negatively affects semen parameters and sperm morphology. These effects appear to be dose- and recipient age– dependent, and an inverse correlation between HU treatment duration and semen variables was suggested (14). HU-induced azoospermia is reversible after drug cessation, although sperm parameters do not recover to baseline values. In order to treat iron overload, our patient received the iron chelator desferrioxamine. There are a few reports which suggest that desferrioxamine may be associated with suppression of spermatogenesis (6).

Our patient developed hepatitis C infection, which was attributed to transmission from blood transfusions prior to universal screening in 1990. Chronic hepatitis C may impair male fertility at the level of the testis by decreasing cFT and inhibin B levels, impairing semen quality (15). A positive correlation between serum viral load and hepatitis C virus concentration in semen has been suggested (16) but is as yet unproven. Successful antiviral treatment improves spermatogenesis (15), but combining pegylated interferon-alpha with ribavirin, as given to our patient, may worsen hepatitis C–induced infertility. Ribavirin is known to accumulate in human seminal fluid (16), but its gonadotoxic mechanism is unclear. Successful pregnancies within 3 months of discontinuation of ribavirin in the male partner demonstrate the reversibility of its gonadotoxicity. However, the miscarriage rate was shown to be 33.3% among the pregnancies with known outcomes, suggesting extended effects of ribavirin on sperm quality and fetal outcome (17).

The immunosuppressive therapies and the whole body radiation our patient received for HSCT could also have contributed to his hypogonadism. Immunosuppressants may impair spermatogenesis and reduce male fertility. CD52, the target of alemtuzumab, a lymphocyte-depleting agent used in transplantation settings, is a surface antigen on lymphocytes and other white blood cell subtypes and on mature sperm (18) and is also found in seminal fluid. Male reproductive tract–CD52 plays a role in semen coagulation and liquefaction and is detected in 80% of ejaculated sperm. In vitro anti-CD52 antibodies increase spermatozoa agglutination and decrease motility and viability. However, to date, similar findings have not been reported in vivo, leaving the effects of alemtuzamab on fertility unclear in our patient.

Sirolimus (rapamycin) is an immunosuppressant that prevents T and B cell activation by inhibiting their responses to interleukin-2. Sirolimus interferes with cell cycle progression and proliferation of spermatogonia. Sirolimus exposure results in diminished testicular function with lower free testosterone levels and increased LH, FSH, and SHBG levels, as well as testicular atrophy, reduction of sperm count, decreased sperm motility, and decreased clinical fertility (19). Discontinuing the drug was shown to improve sperm parameters in rats and humans (19).

Finally, TBI, here performed as part of a pretransplantation conditioning regimen, is well known to have adverse effects on gonadal function in both genders. Spermatogenesis is particularly sensitive to radiation. The adverse effects and recovery are dose-dependent (10,20). Permanent loss of fertility can result from exposure of testes to fractionated doses as low as 1.4 to 3.0 Gy (20). Various types of testicular shielding have been developed to decrease scrotal radiation doses, optimally to below 1 Gy, to protect the testicular germinal epithelium. In our patient, a standard two-sided clam shell scrotal shield was used. However, this type of shielding does not nullify scrotal radiation exposure due to entry of radiation through the slits and the presence of scatter radiation within the clam shell (10).

Evaluation of the reproductive function in male patients with SCD after nonmyeloablative conditioning and allogeneic HSCT has to the best of our knowledge not yet been reported. Our patient had secondary with possible coexisting primary hypogonadism due to SCD, hepatitis C, and their treatments (Table 2). The severity of testicular atrophy suggested considerable damage to seminiferous tubules and perhaps the Leydig cells. Restoration of his reproductive capacity was therefore particularly challenging.

Conventionally, hypogonadism is treated with testosterone replacement to restore libido and sexual function. However, for patients who desire fertility and who have predominantly central hypogonadism, testicular stimulation with pituitary gonadotropins may be given to stimulate spermatogenesis. hCG/LH stimulates the Leydig cells to produce high levels of intratesticular testosterone required to initiate spermatogenesis. Those with profound hypogonadotropic hypogonadism, such as our patient, are usually treated with FSH (hMG or recombinant FSH) in addition to hCG/LH. FSH acts on the Sertoli cells to facilitate the last step of spermatogenesis, thus producing mature sperm from spermatids. Recovery of spermatogenesis followed by natural conception may occur within 10 to 12 months of treatment, but, if infertility persists, assisted reproductive techniques may be required.

Our patient, despite a complicated past medical history and long-term immunosuppression, regained his fertility after treatment of his hypogonadotropic hypogonadism, although testicular size was not fully restored.

CONCLUSION

This patient’s experience supports the hypothesis that SCD and its treatments followed by the HSCT conditioning regimen and associated medications do not irreparably impair spermatogenesis. Nonetheless, as treatment for patients with SCD improves, prolonging their life expectancy, it is important to be mindful of the potential for infertility, particularly

in males. We therefore suggest offering pretreatment semen cryopreservation early in the male patient's management, as this approach remains to date the only readily available and effective choice for fertility preservation.

ACKNOWLEDGMENT

We thank Drs. Monica Skarulis and Smita Abraham for helpful discussions during the treatment of our patient. We thank Dr. Antonio T. Fojo for critical comments and help with editing the manuscript.

Abbreviations

cFT	calculated free testosterone
cGy	centigray
FSH	follicle-stimulating hormone
Gy	gray
hCG	human chorionic gonadotropin
HSCT	hematopoietic stem cell transplantation
HU	hydroxyurea
LH	luteinizing hormone
SCD	sickle cell disease
SCT	stem cell transplantation
SHBG	sex hormone– binding globulin

REFERENCES

1. Bruno D, Wigfall DR, Zimmerman SA, Rosoff PM, Wiener JS. Genitourinary complications of sickle cell disease. J Urol. 2001; 166:803–811. [PubMed: 11490223]
2. Taddesse A, Woldie IL, Khana P, et al. Hypogonadism in patients with sickle cell disease: central or peripheral? Acta Haematol. 2012; 128:65–68. [PubMed: 22678347]
3. Bomhard EM, Gelbke HP. Hypoxaemia affects male reproduction: a case study of how to differentiate between primary and secondary hypoxic testicular toxicity due to chemical exposure. Arch Toxicol. 2013; 87:1201–1218. [PubMed: 23430139]
4. Brewer G. Zinc supplementation treatment of growth retardation and hypogonadism in sickle cell patients. Am J Hematol. 1981; 10:195–198. [PubMed: 7234864]
5. Bajoria R, Chatterjee R. Hypogonadotrophic hypogonadism and diminished gonadal reserve accounts for dysfunctional gametogenesis in thalassaemia patients with iron overload presenting with infertility. Hemoglobin. 2011; 35:636–642. [PubMed: 22035015]
6. De Sanctis V, Borsari G, Brachi S, Govoni M, Carandina G. Spermatogenesis in young adult patients with beta-thalassaemia major long-term treated with desferrioxamine. Georgian Med News. 2008:74–77. [PubMed: 18403814]
7. Berthaut I, Guignedoux G, Kirsch-Noir F, et al. Influence of sickle cell disease and treatment with hydroxyurea on sperm parameters and fertility of human males. Haematologica. 2008; 93:988–993. [PubMed: 18508803]
8. Vuong C, Van Uum SH, O'Dell LE, Lutfy K, Friedman TC. The effects of opioids and opioid analogs on animal and human endocrine systems. Endocr Rev. 2010; 31:98–132. [PubMed: 19903933]

9. Tauchmanovà L, Selleri C, Rosa GD, et al. High prevalence of endocrine dysfunction in long-term survivors after allogeneic bone marrow transplantation for hematologic diseases. Cancer. 2002; 95:1076–1084. [PubMed: 12209694]
10. Kinsella TJ, Trivette G, Rowland J, et al. Long-term follow- up of testicular function following radiation therapy for early-stage Hodgkin's disease. J Clin Oncol. 1989; 7:718–724. [PubMed: 2497228]
11. Hsieh MM, Kang EM, Fitzhugh CD, et al. Allogeneic hematopoietic stem-cell transplantation for sickle cell disease. N Engl J Med. 2009; 361:2309–2317. [PubMed: 20007560]
12. Au WY, Lam WM, Chu WC, et al. A magnetic resonance imaging study of iron overload in hemopoietic stem cell transplant recipients with increased ferritin levels. Transplant Proc. 2007; 39:3369–3374. [PubMed: 18089387]
13. Smith HS, Elliott JA. Opioid-induced androgen deficiency (OPIAD). Pain Physician. 2012; 15(suppl 3):ES145–ES156. [PubMed: 22786453]
14. Lukusa AK, Vermylen C, Vanabelle B, et al. Bone marrow transplantation or hydroxyurea for sickle cell anemia: long-term effects on semen variables and hormone profiles. Pediatr Hematol Oncol. 2009; 26:186–194. [PubMed: 19437321]
15. Durazzo M, Premoli A, Di Bisceglie C, et al. Alterations of seminal and hormonal parameters: an extrahepatic manifestation of HCV infection? World J Gastroenterol. 2006; 12:3073–3076. [PubMed: 16718790]
16. Hofer H, Donnerer J, Sator K, et al. Seminal fluid ribavirin level and functional semen parameters in patients with chronic hepatitis C on antiviral combination therapy. J Hepatol. 2010; 52:812–816. [PubMed: 20399525]
17. Hong Z, Cameron CE. Pleiotropic mechanisms of ribavirin antiviral activities. Prog Drug Res. 2002; 59:41–69. [PubMed: 12458963]
18. Hale G, Rye PD, Warford A, Lauder I, Brito-Babapulle A. The glycosylphosphatidylinositol-anchored lymphocyte antigen CDw52 is associated with the epididymal maturation of human spermatozoa. J Reprod Immunol. 1993; 23:189–205. [PubMed: 7685389]
19. Zuber J, Anglicheau D, Elie C, et al. Sirolimus may reduce fertility in male renal transplant recipients. Am J Transplant. 2008; 8:1471–1479. [PubMed: 18510638]
20. Ash P. The influence of radiation on fertility in man. Br J Radiol. 1980; 53:271–278. [PubMed: 6991051]

Table 1

Patient Hormonal Levels Before and After Infertility Treatment

Weeks before (−) and after (+) starting infertility treatment	FSH (normal, 1–9 mIU/mL)	LH (normal, 1–9 mIU/mL)	TT (normal, 300–1,000 ng/dL)	cFT (normal, >7 ng dL)	SHBG (normal, 13–71 nmol/L)
−5	4.1	5.4	262	1.9	128
+4			892	9.3	94
+10.5	4.8	2.9	607	6.6	90
+14			594	5.7	97

Abbreviations: cFT = calculated free testosterone; FSH = follicle-stimulating hormone; LH = luteinizing hormone; SHBG = sex hormone–binding globulin; TT = total testosterone.

Endocr Pract. Author manuscript; available in PMC 2016 January 04.

Table 2

Patient Ejaculatory Volume, Sperm Count and Mobility, and Testicular Volume Before and After Infertility Treatment

Weeks before (−) and after (+) starting infertility treatment	EV (mL) (normal, 1–5)	TSC ($\times 10^6$/ejaculate) (normal, $\geq 40 \times 10^6$)	Percent MS (normal, 50–80)	RTV (mL) (normal, 17–32)	LTV (mL) (normal, 17–32)
−5	0.9	0	0	5	5
+4	1.9	0.76	51	6	7
+8	1.2	0.84	28	7	6
+14	2.0	4.8	40	6	7

Abbreviations: EV = ejaculate volume; LTV = left testicular volume; MS = mobile sperm; RTV = right testicular volume; TSC = total sperm count.