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LETTER TO THE EDITOR

Paternity after directed collection of testicular sperm for *in vitro* fertilization after BMT for hematological malignancies

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Allogeneic and autologous BMT are routine treatments for many men with advanced hematologic cancers. Although associated with excellent survival rates, myeloablative conditioning regimens consisting of high-dose combination alkylating agents and TBI in cases of allogenic transplants are generally thought to result in permanent infertility in the vast majority of patients undergoing BMT.[1] As a consequence, patients who survive and enter their reproductive years have limited opportunities for fatherhood if they were not old enough to, or able to, bank sperm before to induction of therapy.

From our review of the English literature, there are eight reported cases of paternity after BM conditioning and BMT. Seven men established paternity after spontaneous recovery of natural fertility[2–4] and one achieved paternity with the use of assisted reproduction (ART).[5] We present two novel cases of biological paternity using testis sperm and assisted reproduction in men without sperm in the ejaculate (azoospermia) after BMT for hematologic malignancies.

Case 1 is a 38-year-old patient who presented for fertility care with persistent azoospermia after aggressive chronic myelogenous leukemia (CML) treatment. He was diagnosed with CML 7 years prior to presentation and initially treated with hydroxyurea and α-IFN. The addition of low-dose cytarabine subsequently induced disease remission. The patient experienced a blast crisis 2 years later that was treated with plicamycin, high-dose cytarabine, etoposide and hydroxyurea. The patient attempted to bank sperm before this treatment, but a semen analysis showed azoospermia. This blast crisis did not resolve and the patient then received decitabine and daunorubicin followed by total-body irradiation and allogeneic BMT (HLA-B mismatch, unrelated donor). Six months post-transplant the patient developed steroid responsive GVHD. He was subsequently medically managed and presented for fertility care 4.5 years after the transplantation, on carvedilol and verapamil for chemotherapy-induced cardiomyopathy, trimethoprim/sulfamethoxazole and topical 5-fluorouracil for disseminated actinic superficial porokeratosis (DASP).

On physical examination he appeared healthy. Scrotal examination revealed a normal phallus and small, soft testicles (10 ml right; 12 ml left). The vasa deferentia and epididymides were palpably normal. No clinical varicocele or adenopathy was apparent. Laboratory examination was significant for azoospermia on two consecutive semen analyses with centrifuged pellet analysis, an elevated follicle-stimulating hormone (FSH) of 18.6 IU/l (normal 2–8 IU/l), a LH of 6.9 IU/l (normal 2–12 IU/l and a testosterone of 641 ng/100 ml (normal 241–800 ng/100 ml).

To assess whether usable testicular sperm might be present to use with assisted reproduction, the patient underwent bilateral testicular fine needle aspiration (FNA) 'mapping' with 15 cytologic specimens taken from each testis.[6] FNA mapping revealed three areas containing mature sperm (Figure 1a). The remaining 27 sites revealed germ cell aplasia. Four months later, the patient underwent bilateral microdissection testicular sperm extraction that focused sperm retrieval on the earlier map locations. Thirteen small biopsies were obtained that provided sufficient sperm for all oocytes during *in vitro* fertilization (IVF) and intracytoplasmic sperm injection (ICSI) and sperm cryopreservation.[7] At IVF, seven embryos were obtained after fertilization and four were implanted. The couple delivered healthy twins, one male and one female.

Case 2 is a 33-year-old patient who had a history of childhood Hodgkin's disease and was referred for evaluation of infertility and azoospermia. He was diagnosed with Hodgkin's disease (Stage IIB) at age 12. He was treated with chemotherapy (MOPP, ABVD) and radiotherapy with consequent disease remission. At age 17, he relapsed and underwent a CBV conditioning regimen followed by reinduction with two cycles of MOPP/AV hybrid chemotherapy and autologous BMT. Upon presentation for fertility care, the patient was in CR with residual acid reflux under good control. A physical examination revealed a healthy, well developed male with small testes (12 ml right; 12 ml left) of normal consistency. A left grade II varicocele was observed. A routine semen analysis was significant for normal volume azoospermia. No sperm were found on centrifuged pellet analysis. Endocrine parameters revealed an FSH of 25.0 IU/l, LH of 6.6 IU/l and a testosterone of 566 ng/100 ml.

Again, to determine the patient's candidacy for assisted reproduction testicular FNA 'mapping' was performed under local anesthesia in the office. The diagnostic FNA procedure revealed mature spermatozoa in 3 of 30 sites sampled (Figure 1b). Nine months later the patient underwent microdissection testicular sperm extraction under local anesthesia and i.v. sedation that focused on sperm retrieval to FNA map locations showing sperm. Sufficient motile sperm were isolated to cover all eggs at IVF, and extra sperm were cryopreserved. At IVF, six mature eggs were harvested from the patient's 33-year-old partner. ICSI resulted in two fertilized eggs that were implanted and an ongoing clinical singleton pregnancy was established.

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