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# **Successful testicular sperm extraction after hematopoietic stem cell transplantation: a case series**

**Authors :** Ludmilla Ogouma Aworet<sup>1</sup>, Rahaf Haj Hamid<sup>1</sup>, Diane Rivet Danon<sup>1,2</sup> Isabelle Berthaut<sup>1,3</sup>, Anna Ly<sup>1</sup>, Guillaume Bachelot<sup>2</sup>, Marie Prades<sup>1</sup>, Kamila Kolanska<sup>1</sup>, Valentine Frydman<sup>4</sup>, Rachel Lévy<sup>1,3</sup>, Nathalie Sermondade<sup>1,3</sup>, Charlotte Dupont<sup>1,3</sup>

## **Affiliations :**

<sup>1</sup> Reproductive Biology and CECOS, Tenon Hospital (AP-HP), Sorbonne-Université, 75020 PARIS, France

<sup>2</sup> Reproductive Biology and CECOS, Cochin Hospital (AP-HP), Université Paris centre, 75014 PARIS, France

<sup>3</sup> Sorbonne University, Research center Saint-Antoine, Inserm US938, 75012 PARIS, France

<sup>4</sup> Urology department, Hôpital Tenon (AP-HP), Sorbonne-Université, 75020 PARIS, France

## **Correspondence :**

Dr L OGOUMA AWORET ([ludmilla.ogoumaaworet@aphp.fr](mailto:ludmilla.ogoumaaworet@aphp.fr)),

Service de Biologie de la Reproduction CECOS, Hôpital Tenon (AP-HP), Sorbonne-Université, 4 rue de la Chine, 75020 PARIS, France

**Running title:** TESE after hematopoietic stem cell transplantation

Dear Editor,

Allogeneic or autologous hematopoietic stem cell transplantation (HSCT) concerns an increasing number of patients. Worldwide, 89 070 allogeneic and autologous HSCT procedures were reported in 2016, representing a 7% increase per year since 1991.<sup>1</sup> Improved transplant strategies and therapeutic efficacy have made HSCT a curative option for various indications, mostly comprising malignant blood cell pathologies but also including solid tumours or benign conditions.<sup>2</sup> The conditioning regimen for transplantation often includes alkylating agents and/or total body irradiation (TBI).<sup>2</sup> These treatments usually lead to permanent infertility.<sup>3</sup> In men, the consequences include the impairment and reduction of Sertoli and Leydig cells, leading to the suppression of the spermatogonia pool and increased release of gonadotrophin.<sup>3</sup> Although sperm banking can mitigate the risk of infertility,<sup>3</sup> it is not always possible or even proposed to patients before the initiation of gonadotoxic treatment. In this context, some very rare cases of recovery of spermatogenesis following HSCT have been described, leading to successful testicular sperm extraction (TESE) followed by intra cytoplasmic sperm injection (ICSI),<sup>4-5</sup> or even spontaneous conception.<sup>6</sup> Nevertheless, most studies gauging male fertility after HSCT did not report spermatogenesis or conception.<sup>7</sup> Given these data, most fertility specialists propose sperm donation to patients who did not benefit from previous fertility preservation approaches.

Here, we report three cases of successful TESE in patients who were in remission from a hematologic pathology following HSCT. These are the only TESEs performed in this context at our centre at Tenon hospital (Paris, France) since 2010. ICSI was performed for the three patients and their partners, resulting in a pregnancy and live births. A local ethics committee

(IRB CLEA-2020-163) approved the study protocol on 18 December 2020. All patients consented for the study.

## **Case 1**

In 2002, a 26-year-old patient was diagnosed with large B-cell lymphoma with gastric localization. He underwent surgery for gastrectomy and was treated with various chemotherapies. In November 2002, he received a conditioning BEAM protocol (carmustine, etoposide, cytosine-arabiosine and melphalan) for autologous HSCT. No sperm cryopreservation was possible prior to the treatments and, in 2012, the patient sought a fertility check-up. Azoospermia was diagnosed. At this time, his follicle stimulating hormone (FSH) level was 33.9 mUI/mL (N: 1.5 to 12.4 mUI/ml), luteinizing hormone (LH) was 6.0 mUI/mL (N: 1.7 to 8.6 mUI/ml), total testosterone was 10.6 ng/ml (N: 2.5 to 10.0 ng/ml) and prolactin was 7.4 ng/ml (N: 4.0 to 15.3 ng/ml). As the patient had never fathered a child, bilateral conventional TESE was proposed. Spermatozoa were found in both testis and were cryopreserved. Histological analysis showed Sertoli-cell-only syndrome for two-thirds of the seminiferous tubes and active spermatogenesis was detected in the remaining one-third. In 2016, the 40-year-old patient and his 27-year-old wife planned to start a family. Azoospermia was confirmed, and his wife's check-up did not reveal any fertility issues. An ICSI attempt was planned using the cryopreserved testicular spermatozoa. Three good-quality embryos were obtained. A fresh embryo transferred on Day 3 did not result in a pregnancy. Transfers of two frozen-thawed embryos were performed successively and resulted in the full-term births of two healthy babies. As of today, both children exhibit normal psychomotor development.

## **Case 2**

A 27-year-old man was diagnosed with acute myeloid leukaemia in November 2012. He immediately received induction chemotherapy with idarubicin and cytarabine. Due to the urgency of treatment, he could not undergo a fertility preservation procedure. In early 2013, consolidation chemotherapy, also including idarubicin and cytarabine, was prescribed. It was decided that the patient would undergo allogeneic HSCT following busulfan and cyclophosphamide conditioning treatment in April 2013. Remission was confirmed after follow-up visits conducted twice a year, and anti-rejection treatment (methotrexate and ciclosporin) was completed in 2015.

In 2019, the 34-year-old patient and his 33-year-old nulliparous partner wished to start a family. A fertility check-up revealed severe cryptozoospermia, without any motile spermatozoa, in the patient and polycystic ovary syndrome (PCOS) in the female partner. After a multidisciplinary meeting, it was decided that TESE would be proposed. The patient's reproductive functions were evaluated. The patient presented a normal karyotype without Y chromosome microdeletion. The FSH level was 11.2 mUI/mL (N: 1.5 to 12.4 mUI/ml), LH level was 2.5 mUI/mL (N: 1.7 to 8.6 mUI/ml), total testosterone level was 2.3 ng/ml (N: 2.5 to 10.0 ng/ml) and inhibin B level was 30.0 pg/ml (N: 135.0 to 350.0 pg/ml). Testicular ultrasound showed a moderate unilateral varicocele. Bilateral micro-TESE permitted the cryopreservation of a few motile spermatozoa. Histological analysis revealed Sertoli-cell-only syndrome. Two ICSIs using testicular spermatozoa enabled the freezing of two blastocysts. Frozen-thawed transfers resulted in one miscarriage. Before the third attempt, semen parameters were assessed and an improvement in the form of a few motile spermatozoa was observed. Fresh spermatozoa collection was proposed on the day of oocyte pick-up for ICSI, and a few motile spermatozoa were available. A Day-5 blastocyst was frozen. The subsequent frozen embryo transfer resulted in the delivery of a healthy baby boy after a C-section at 38 weeks of

amenorrhea. The C-section resulted from a foetal arrhythmia. As of today, the child exhibits normal psychomotor development.

### **Case 3**

A 35-year-old patient was diagnosed with Philadelphia chromosome-like acute lymphoblastic leukaemia in 2015 following the onset of chronic myeloid leukaemia in 2010. The induction treatment comprised imatinib and dexamethasone, followed by consolidation chemotherapy including cytarabine and methotrexate. Finally, allogeneic HSCT with the T1B3F-SAL conditioning protocol (fludarabine, busulfan and anti-thymocyte globulin) was proposed to the patient. Fertility preservation was planned at our fertility centre but the patient presented with azoospermia. In 2016, he underwent encephalic irradiation. The anti-rejection treatment (ciclosporin) was completed in July 2017 and imatinib was stopped in August 2018. Six months later, in March 2019, the patient and his partner wished to start a family. The patient's partner was 35 years old and presented with PCOS. Azoospermia was confirmed after two sperm collections. Testicular ultrasound showed bilateral testicular atrophy. The FSH level was 30.0 mUI/mL (N: 1.5 to 12.4 mUI/ml), LH level was 14.6 mUI/mL (N: 1.7 to 8.6 mUI/ml), inhibin B level was less than 15.0 pg/ml (N: 135.0 to 350.0 pg/ml) and total testosterone level was 3.2 ng/ml (N: 2.5 to 10.0 ng/ml). The karyotype was 46XY, and no Y chromosome microdeletions were observed. The multidisciplinary staff decided to propose TESE. Micro-TESE was conducted in January 2021 and facilitated the collection of motile spermatozoa that were cryopreserved. Histological analysis revealed hypospermatogenesis. ICSI was carried out using the frozen testicular spermatozoa. One Day-5 blastocyst was frozen and then thawed for transfer. A pregnancy is currently ongoing.

### **Discussion**

TESE can be suggested for patients in remission from a malignant disease who did not benefit from fertility preservation before gonadotoxic treatments and who present with prolonged azoospermia after remission. A recent review<sup>8</sup> showed that testicular spermatozoa could be retrieved in about 50% of such cases. However, the chances of successful retrieval vary according to the diagnosis and hence, the type and intensity of the treatment. This review found very few studies with patients who underwent HSCT, and only one study reported on a patient who underwent a successful sperm extraction after HSCT.<sup>5</sup> Due to the lack of data in the literature, very few physicians propose TESE after HSCT. The three patients described in this study are the only ones who underwent TESE after HSCT at our centre. Although all three patients had positive results, it is important to note that these cases cannot prove the efficacy of TESE in such contexts. Nevertheless, these three cases show that TESE is worth considering in such contexts. However, it is important to assess the benefit-risk ratio as there are no prognostic markers that may help in decision-making. Indeed, FSH level is usually used as a prognostic marker before TESE<sup>9</sup> but the three patients presented elevated FSH levels, with two of them having levels higher than 30.0 UI/L. The time necessary for the potential recovery of spermatogenesis after a gonadotoxic treatment is unknown and unpredictable. This time may depend on the dose of radiation and the type and dose of chemotherapies. Fractionated radiation for 3 to 4 weeks is a cause of greater delay in recovery or azoospermia.<sup>10</sup> Unfortunately, we could not access important information on the chemotherapy doses administered to the three patients described here. The gap between HSCT and successful TESE ranged from 5 to 10 years.

In conclusion, TESE can be considered for patients who have undergone bone marrow transplantation. Without objective prognostic criteria, the benefit-risk ratio needs to be

carefully evaluated on a case-by-case basis. More research is necessary to improve our knowledge regarding this topic.

#### **Author contributions**

LOA collected the data. IB, AL, GB, MP, VF, KK and RL cared for the patient and collected clinical information. LOA, CD, NS, RHH and DRD wrote the manuscript. All authors read and approved the final manuscript.

#### **Competing interests**

All authors declare no competing interests.

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