A male phenotype (XY) hermaphrodite treated for seminoma, fathered a healthy child by IVF–ICSI technique

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Received: 9 May 2008 / Accepted: 25 June 2008 / Published online: 22 July 2008
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Abstract

Objective To report a successful delivery of a healthy infant fathered by an infertile 46, XY true hermaphrodite who suffered from a seminoma.

Design Case report

Setting IVF unit in University hospital

Patient(s) Male 41 years (true hermaphrodite), his wife 35 years

Main Outcome Measures Laboratory, pathology tests and ultrasound tests

Results The above patient treated and cured from seminoma, the couple had in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) using frozen testicular sperm and had a healthy baby.

Conclusion This is the first case report of a successful delivery of a healthy infant fathered by an infertile 46, XY true hermaphrodite who suffered from a seminoma. Once treated and cured, the couple had IVF and ICSI using frozen testicular sperm and had a healthy baby.

This is a case report, written retrospectively, no funding or conflict of interests involved.

Capsule This is the first case report of a successful delivery of a healthy infant fathered by an infertile 46, XY true hermaphrodite who suffered from a seminoma. Once treated and cured, the couple had IVF and ICSI using frozen testicular sperm and had a healthy baby.

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Keywords Hermaphrodite · Seminoma · IVF · ICSI

Introduction

Assisted reproductive technology has improved to the extent of achieving pregnancies for severely infertile couples. In particular, the intracytoplasmic sperm injection (ICSI) technique rescues not only severely oligospermic but also azoospermic males.

Although a true hermaphrodite is uncommon, it has been reported in more than 400 individuals [5]. It is generally known that almost all hermaphrodites are infertile, however, German et al. [6] observed spermatogenesis in an hermaphrodite. Tumours arising in the gonads of true hermaphrodites is a very rare finding and only very few cases have been reported in the literature.

To the best of our knowledge this is the first case report of a successful delivery of a healthy infant fathered by an infertile 46, XY true hermaphrodite who suffered from seminoma. Once treated and cured, the couple had in vitro fertilization (IVF)–ICSI using frozen testicular sperm, then had a healthy live baby.

Case report

In 2004, a 35-year-old woman and her 41-year-old husband were referred to our IVF clinic (assisted conception unit at King Abdullah University Hospital). The couple had been trying to achieve a pregnancy for more than 16 years. The wife's physical, gynecological examinations, hormonal studies and ultrasound were suggestive of polycystic ovary disease, she had a normal hysterosalpingogram.

The husband was seen in 2001 by urologist for infertility and impalpable right testis, on examination confirmation of impalpable right testis and ultrasound examination revealed pelvic mass of 7×6 cm in the right side of the pelvis. He had laparotomy, and right sided orchidectomy of a right testicular seminoma which was excised in addition to what appeared as a uterus and tubes in 2001. The pathology report showed a seminoma mass with a uterus and Fallopian tubes and some ovarian tissue. He was diagnosed as a true hermaphrodite. Metastatic work-up showed no involvement in the parenchymal organs along with tumour markers as alpha fetoprotein, B-human chorionic gonadotropin (hCG) were within normal limits. After surgery he received an adjuvant radiotherapy and his semen analysis showed azoospermia. His chromosomal analysis was XY and no Y microdeletion was found. Complete recovery was achieved but azoospermia was again ascertained in his ejaculate.

The couple sought infertility treatment. To start, the couple had prior genetic and infertility counseling then a testicular biopsy was carried out on the husband left testis in March 2004 and it showed hyalinization of most seminiferous tubules with few seminiferous tubules showing evidence of spermatogenesis with no sperm formation. Testicular sperm extraction (TESE) was performed in January, 2005 and showed very few immotile and abnormal forms and few motile sperm. The specimen was divided into several aliquots and cryopreserved in liquid nitrogen.

The couple were prepared for IVF–ICSI treatment and during the first treatment cycle in February, 2005 11 oocytes were retrieved, and ten of 11 were fertilized by ICSI using frozen sperm from the testicular biopsy performed in January, 2005. Three embryos (one grade 1 and two grade 2), which had developed to the eight-cell stage, were transferred. She developed mild ovarian hyperstimulation syndrome and was admitted to hospital for few days, however a pregnancy did not ensue. A second attempt was made in April, 2005; third and fourth attempts were performed in July, 2005 and January, 2006 which ended with embryos similar in number and quality, but with no pregnancy.

In 2006 the husband married a divorced woman of 35 years who had previously had a child. She had one attempt of IVF–ICSI in May, 2006; six mature oocytes

were retrieved using the short protocol. Ovarian stimulation was achieved by combined administration of GnRH agonist, FSH. GnRH-a was administered for 12 days from the second day of menses, FSH was given until the dominant follicle reached a mean diameter of 18 mm, and then 10,000 units of hCG was administered. Vaginal ultrasound-guided follicle puncture took place 35 h after the hCG injection and six oocytes were retrieved. The frozen sperm specimen was thawed. Few slightly motile sperm were found, but only one had normal morphology. Four of the six oocytes were fertilized by ICSI and they developed to the eight-cell cleavage stage 72 h after insemination and three embryos (two grade 1 and one grade 2) were subsequently transferred. After that the patient was given luteal support, an hCG injection once weekly and oral progestogen daily. The quantitative blood β -hCG level 14 days after embryo transfer was positive, 172 IU/l. At 6 weeks of gestation, a singleton pregnancy and fetal heartbeat were confirmed by transvaginal ultrasound. The couple opted to refuse amniocentesis. She had uneventful antenatal care and was scheduled for elective Caesarean section at 38 weeks. Caesarean section was performed in January, 2007 and she delivered a live healthy female weighing 3 kg.

Discussion

A true hermaphrodite has with functional gonadal tissue (testis and ovary) of each sex and is comparatively rare. It needs the demonstration of both well-differentiated testicular and ovarian tissue [1] to support the diagnosis. In most patients, the external genitalia are ambiguous but masculinized to variable degrees, and 75% are raised as male. The testis or ovotestis may reside at any point along the path of testicular descent. Testes are more commonly located on the right side [2]. Only a few cases have been reported in the literature of tumours arising in the gonads of true hermaphrodites [3]. The incidence of gonadal tumors is approximately 10% in 46, XY true hermaphroditism and 4% in 46, XX true hermaphroditism. Both gonadoblastoma and dysgerminoma have been described [4].

Although a true hermaphrodite is uncommon, it has been reported in more than 400 individuals [5]. It is generally known that almost all hermaphrodites are infertile, however, German et al. [6] observed spermatogenesis in an hermaphrodite. Furthermore, in abstract, both Inatomi et al. [7] and Manba et al. [8] have reported the delivery of infants fathered by a true hermaphrodite under natural conditions in Japan.

Because both gonads are functioning, true hermaphrodites show a wide range of morphological anomalies such as a phenotypic male with an ovary on one side and

ovotestis on the other. Our patient had a karyotype confirming a 46XY constitution. The location, size and extent of the tumour in our patient required adjuvant therapy in addition to excision as the established treatment for low-stage seminoma is inguinal orchidectomy followed by therapeutic or adjuvant radiation therapy. This treatment is a highly effective method of treating low-stage disease with minimal morbidity.

Several articles have recently pointed out a correlation between infertility and testicular cancer [9, 10]. According to some authors, a dysgenetic syndrome links infertility and testicular cancer [11]. In patients with non-obstructive azoospermia or obstructive azoospermia that cannot be corrected, the only possibility of fertilization is provided by sperm retrieval by TESE [12].

Semen cryopreservation pre-orchidectomy is clearly the method of choice for testicular cancer in fertile patients [13].

This case demonstrates that young male cancer patients have a greatly improved chance of fatherhood after completing their oncology treatment, thanks to new methods in assisted reproduction. Modern oncology treatment by surgery, chemotherapy and radiotherapy makes long-term survival a reality for the majority of patients. However, the use of ICSI requires only a few motile, i.e. living, sperm cells. This method of directly injecting a single sperm into a mature oocyte is professionally and technically very demanding, but markedly improves the chances of fatherhood for men who previously had none. It is therefore expedient to freeze all ejaculates, regardless of the inferior quality of the sample.

Novero et al. [14] described the first successful pregnancy using ICSI of fresh sperm obtained from cryopreserved-thawed testicular tissue (TESE) from a patient with azoospermia having a seminoma as an incidental finding. He emphasized the importance of histological diagnosis in order to exclude malignancy on the other side. Res et al. (2000) described a similar case [15]. The incidence of malignant tumours in infertile men is 0.4–1.1%. The ejaculate in non-seminoma testicular tumours is statistically significantly inferior to the ejaculate in seminoma patients [16].

Seminoma is a tumour of the undeveloped germ cell. The spermatozoa used for ICSI was a mature cell, not a malignant cell. However, spermatozoa can carry chromosomal or gene defects and all patients with testicular tumours should remain under long-term supervision.

Some criticism has already been expressed with respect to the use of this method, due to the possible transmission of altered genetic material [17]. However, no definite data exist regarding the transmissibility of testicular tumour from father to son.

It is recommended that peripheral blood karyotyping be carried out in all patients with azoospermia and this was

performed in our patient. There is a possibility of transfer of the *AZF* gene (azoospermia factor), located on the Y chromosome, in non-obstructive azoospermia. Male offspring might thus inherit their father's defect. A distinct increase in spontaneous chromosomal aberrations has been reported [18]. The chromosomal instability may be a factor in the development of malignancy in testicular tumours.

This report describes the birth of the first child in Jordan conceived by means of fertilization with thawed sperm cells from testicular tissue in a true hermaphrodite with a seminoma and azoospermia. The case demonstrates successful co-operation between the IVF Centre, Departments of Urology, Gynaecology and Obstetrics, a pathohistologist and a genetics specialist. It is advisable that patients with testicular tumours, who might later wish to father a child, be offered options prior to the initiation of oncology therapy. These should include deep-freezing of ejaculate, even in cases of very poor quality, and freezing of a biopsy of healthy testicular tissue in cases of azoospermia. The new assisted reproduction techniques offer greatly increased options in the treatment of infertility. Thus, it is now possible for oncology patients under current treatment to become biological fathers.

This case report is a chain of rare incidents: a male hermaphrodite is rare, and to develop a seminoma is another rare incident. Once treated it is rare to continue to have normal spermatogenesis, then to have IVF–ICSI and succeed in having a baby is another rare incident. Sugawara et al. [19] described a successful pregnancy in an hermaphrodite using IVF–ICSI, but he did not develop a seminoma.

To the best of our knowledge, this is the first case report of a successful delivery of a healthy infant fathered by an infertile 46, XY true hermaphrodite who suffered from a seminoma. Once treated and cured, the couple had IVF and ICSI using frozen testicular sperm and had a healthy baby.

Acknowledgements The authors would like to thank all the staff at King Abdullah University Hospital, specially the IVF staff and Dr. Amer Sindiani, who helped obtaining the data needed for this case report.

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