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Onset of azoospermia in man treated with ipilimumab/nivolumab for BRAF negative metastatic melanoma

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ABSTRACT

Azoospermia is classified as the complete absence of sperm in ejaculate and accounts for 10–15% of male infertility. Many anticancer drugs are known to cause defects in spermatogenesis, but the effects of immune checkpoint inhibitor cancer therapy on spermatogenesis remains largely unknown. Presented here is a normozoospermic man (60 million sperm/cc of ejaculate) who received a trial combination treatment of Ipilimumab/Nivolumab to treat BRAF negative, stage IV metastatic melanoma. Two years after the treatment, the patient presented as completely azoospermic. The patient subsequently underwent microdissection testicular sperm extraction, during which no sperm was retrieved, and sertoli-only pathology was elucidated.

Introduction

Infertility is defined as the inability to conceive after twelve months of unprotected intercourse or 6 months of unprotected sex in the setting of advanced maternal age.[1] Infertility affects 8–12% of all couples worldwide, of which male factor accounts for 40–50% of cases.[1] Azoospermia occurs due to an inadequate production of spermatozoa, such that spermatozoa are totally absent from the ejaculate, and can appear through pharmacological origins.[2]

Several anti-neoplastic agents have been identified that impair spermatogenesis and decrease sperm count including dabrafenib, a BRAF inhibitor used to treat metastatic melanomas containing a mutated Raf gene.[2] For metastatic melanomas lacking the BRAF mutation, Nivolumab, a PD-1 monoclonal antibody, and Ipilimumab, a cytotoxic T-lymphocyte antigen-4 (CTLA-4) monoclonal antibody, were FDA approved as a combination therapy in 2015.[3] These drugs, known as immune checkpoint inhibitors (ICI), mediate tumor destruction through potentiation of the T-cell anti-tumor response via the removal of coinhibitory signaling. However, the effect of Ipilimumab/Nivolumab treatment on spermatogenesis remains largely unknown. Here we present a case in which a previously normozoospermic man became azoospermic after receiving Ipilimumab/Nivolumab therapy for metastatic melanoma.

Case presentation

Here we present a 30 year-old-male who was diagnosed with mediastinal adenopathy on physical examination. He subsequently underwent a PET-CT scan which delineated multiple enlarged hypermetabolic lymph nodes (the largest being 2.4 × 3.0 cm) localized in the aortopulmonic mediastinum and left hilum, along with pleural findings. A lymph node biopsy was performed via a left anterior thoracostomy which revealed a node positive for melanoma, confirming the diagnosis of stage IV metastatic melanoma. Biopsy of the patient's melanoma revealed an absence of a BRAF mutation.

The patient subsequently began a clinical trial that involved Ipilimumab/Nivolumab combination therapy, which started one month after his diagnosis was confirmed. In the four months that followed, the patient underwent therapy with mycophenolate (2mg everyday) and prednisone for autoimmune hepatitis, during which he developed

Abbreviations: CTLA-4, Cytotoxic T-Lymphocyte antigen-4; ICI, immune checkpoint inhibitor; SA, semen analysis; mTESE, microscopic testicular sperm extraction.

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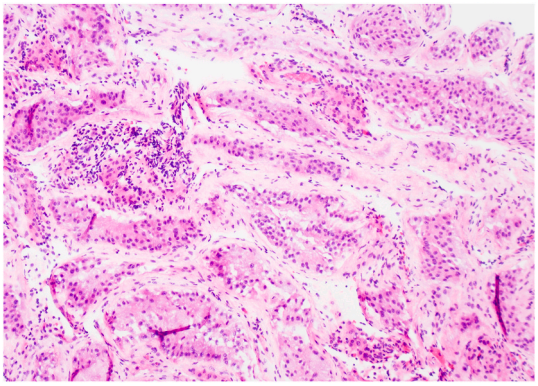

Fig. 1. Sertoli-Only Biopsy (2020) Histology from testicular biopsy during early 2020 mTESE procedure illustrating seminiferous tubules with Sertoli-only pattern and interstitium with Leydig cell hyperplasia (H&E, 10X).

decreased libido that resolved once the treatment had concluded. The patient denied symptoms of orchalgia during therapy and did not visualize any signs of epididymo-orchititis during his ICI therapy. The patient responded to the combination and entered remission, which he has remained in for five years.

Nearly two years after initiation of the patient's ICI treatment, he presented to a urologist for a male factor infertility evaluation. The now 32-year-old patient and his 30-year-old wife, neither of whom had been pregnant prior, had been having unprotected intercourse for two years trying to achieve pregnancy. The patient had previously demonstrated normozoospermia eleven years prior as part of an evaluation for testicular pain and small varicocele veins. The semen analysis (SA) yielded 60 million sperm/cc of ejaculate. On re-presentation after ICI therapy, the SA at this time demonstrated normal volume azoospermia despite centrifugation. A genitourinary exam revealed bilaterally descended testes, 18 cc bilaterally. The vas deferens and epididymis were palpable bilaterally. Bilateral varicoceles were also palpated by the urologist; the left varicocele was documented as grade 2. Hormone analysis showed total testosterone of 556.74 ng/dL, FSH of 20.95 mIU/mL, LH of 5.68 mIU/mL, and E2 of 31 pg/mL.

As a result of these exam findings, the urologist recommended a bilateral varicocelectomy. At the time of varicocelectomy a testicular biopsy was performed demonstrating a sertoli-only pathology. Stains were performed to assess for lymphocytes and neutrophils; however, no inflammatory cells were visualized in the peritubular areas of the testis. Six months following the varicocele repair, the SA was repeated, and the patient remained azoospermic.

The patient subsequently underwent a microscopic testicular sperm extraction (mTESE), a procedure performed on azoospermic men with successful sperm retrieval rates of approximately 52% over all populations.[4] Despite an uncomplicated surgery, no viable sperm were obtained. Testicular biopsy from the procedure once again displayed sertoli-only pathology (Fig. 1).

The patient denied any prior exposure to radiation or chemotherapy. He had no history of epididymitis, orchitis, STIs, or trauma to testicles, and denied any history of testicular torsion, postpubertal mumps, or cryptorchidism. The man had no family history of infertility. The patient's previous medications included alprazolam, crisaborole, desonide, fexofenadine, and meclizine. At the time of follow up, the patient was taking alprazolam, fexofenadine HCL, and omeprazole. These medications have not been linked to male infertility or spermatogenesis.[2,3]

Discussion

It is well understood that chemotherapy may cause deleterious effects on sperm production and fertility. To this end, sperm cryopreservation is an effective fertility preservation technique recommended to postpubertal males receiving certain types of cancer treatment.[5] However, the ever-increasing breadth of anticancer targets has harried the identification of interactions potentially harmful to spermatogenesis. The pathways involved in ICI therapies, such as Ipilimumab/Nivolumab, have been understudied in the scope of male fertility. Here we present a case supporting possible correlation between ICI use and male infertility (Fig. 2).

Although this combination treatment was FDA approved in 2015, a 2016 review found no available evidence in preclinical animal or human data investigating the effect of Nivolumab on infertility.[3] Moreover, the study associated Ipilimumab with positive evidence of fertility risk, citing studies of male monkeys receiving Ipilimumab that yielded evidence of decreased testicular weight without changes to sperm histopathology. Further, in human studies of Ipilimumab, 11% of male and female patients treated exhibited persistent anterior hypophysitis, the portion of the pituitary responsible for gonadotropin production.[3] Nonetheless, the effect of Ipilimumab/Nivolumab on spermatogenesis remains largely unknown.

Conclusion

In the circumstances of the patient presented in this case report, a normozoospermic man (60 million sperm/cc) received a trial treatment of Ipilimumab/Nivolumab to treat BRAF negative, stage IV metastatic melanoma and presented as completely azoospermic two years later. The mTESE preformed five years after the patient's ICI therapy also failed to retrieve any viable sperm. This case report highlights another significant adverse event in spermatogenesis seemingly correlated with ICI use.

Consent

Written consent was obtained from the patient referenced in this case report for the use of health information and chart review.

Declarations of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Author statement

Matthew J. Rabinowitz: Writing - original draft, Investigation, Visualization **Taylor P. Kohn:** Writing - review & editing, Supervision **Vanessa N. Peña:** Writing - review & editing **Iryna V. Samarska:** Resources **Andres Matoso:** Resources **Amin S. Herati:** Conceptualization, Project Administration, Validation.

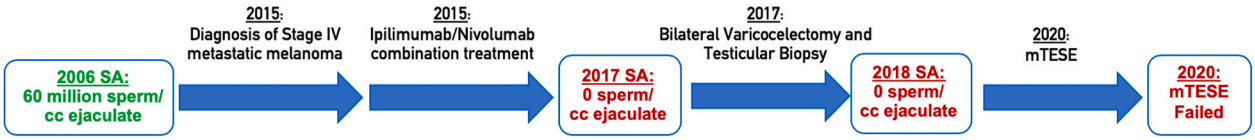

Fig. 2. Case OverviewTimeline of patient's semen analyses (SA), cancer diagnosis and immune checkpoint inhibitor (ICI) treatment (2015), bilateral varicocele repair and testicular biopsy (2017), and microdissection testicular sperm extraction (mTESE) (2020).

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Declaration of competing interest

The authors certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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