

CASE REPORT

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In vitro fertilization pregnancy following treatment of diffuse malignant peritoneal mesothelioma

Viviana de Assis, Jaye Adams, Johanna Hollweg Marowske, Allyson Cochet, Doug Walton, Rhiana Saunders

ABSTRACT

Introduction: Diffuse malignant peritoneal mesothelioma (DMPM) is a rare aggressive neoplasm. Cytoreductive surgery (CRS) and hyperthermic intraoperative peritoneal perfusion chemotherapy (HIPEC) increased overall survivals but the impact on women's fertility after treatment is unknown. **Case Report:** A 28-year-old with primary infertility and recurrent ascites was diagnosed with epithelioid subtype DMPM. Ovarian suppression was achieved with a GnRH-agonist prior to treatment. Two years after remission, she underwent in-vitro fertilization (IVF) and delivered a healthy female infant at term. **Conclusion:** Patients with DMPM have a 50% survival at five years with CRS and HIPEC. We report the rare case of a live birth achieved with IVF following CRS and HIPEC treatment for DMPM. Pre-chemotherapy GnRH

treatment offered ovarian suppression while possibly optimizing fertility preservation.

Keywords: Cytoreductive surgery, Diffuse malignant peritoneal mesothelioma, GnRH agonist therapy, Hyperthermic intraoperative peritoneal perfusion chemotherapy, In-vitro fertilization pregnancy

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Viviana de Assis¹, Jaye Adams², Johanna Hollweg Marowske³, Allyson Cochet³, Doug Walton⁴, Rhiana Saunders⁵

Affiliations: ¹Resident, Department of Obstetrics and Gynecology, San Antonio Military Medical Center, Fort Sam Houston, Texas, USA; ²Faculty, Department of Reproductive Endocrinology and Infertility, Fertility Center of San Antonio, San Antonio, Texas, USA; ³Faculty, Department of Gastroenterology, San Antonio Military Medical Center, Fort Sam Houston, Texas, USA; ⁴Faculty, Department of Pathology, Keesler Air Force Base, Biloxi, Mississippi, USA; ⁵Faculty and Residency Program Director, Department of Reproductive Endocrinology and Infertility, Walter Reed National Military Medical Center, Bethesda, Maryland, USA.

Corresponding Author: Viviana de Assis, DO, CPT, USAF, MC, San Antonio Military Medical Center, Department of Obstetrics and Gynecology, 3551 Roger Brooke Dr., Fort Sam Houston, Texas 78234, USA; Email: Viviana.deassis.mil@mail.mil

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INTRODUCTION

Diffuse malignant peritoneal mesothelioma (DMPM) is a rare yet aggressive neoplasm arising from peritoneal serosal cells. Spreading extensively within the abdominal cavity, DMPM leads to substantial morbidity and mortality [1]. Peritoneal mesothelioma is a rare disease with an estimated 400 new cases per year [2]. Prognosis is poor with unresectable disease; median survival ranges from 10 to 13 months [3]. However, over the past decade, expertise in cytoreductive surgery (CRS) and hyperthermic intraoperative peritoneal perfusion with chemotherapy (HIPEC) has increased for DMPM, leading to an improved overall patient survival. This therapy combination is the recommended treatment for patients with good performance status and no evidence of extra peritoneal disease [4, 5]. With advancing survival rates

and the possibility of cure, it is unknown what impact CRS and HIPEC have on the future fertility of reproductive-aged women. We report an unusual case of a 28 year-old female diagnosed with epithelioid-subtype DMPM who successfully achieved a live birth through in vitro fertilization (IVF) following CRS and HIPEC therapy.

CASE REPORT

A 28-year-old female presented to the Reproductive Endocrinology and Infertility (REI) clinic with a chief complaint of primary infertility. A review of systems revealed abdominal bloating, expanding abdominal girth, and a 15 pound weight gain over the preceding six months. She denied any gastrointestinal or genitourinary complaints. A pelvic ultrasound demonstrated a moderate amount of free fluid within the posterior cul-de-sac (Figure 1). Subsequent magnetic resonance imaging (MRI) revealed a moderate amount of predominantly free fluid tracking superiorly throughout the abdomen (Figure 2).

A transvaginal paracentesis was performed which yielded 200 ml of clear yellow fluid. Fluid cytology was notable only for reactive mesothelial cells. The patient reported symptomatic improvement and desired to continue fertility care. At the time, the working diagnosis was deemed to be a collection of fluid from peritoneal inclusion cysts. Her healthcare provider intended to initiate empiric ovulation induction therapy. However, the care of this patient was interrupted due to an overseas military assignment.

Upon return from a 12-month deployment, the patient represented to continue her fertility evaluation and care. She reported a return of her abdominal distension without significant gastrointestinal or genital-urinary symptoms. Repeat imaging confirmed recurrent diffuse abdominal ascites. A second transvaginal paracentesis was performed, removing 400 mL of clear yellow fluid. Again, benign large reactive mesothelial cells were noted on cytology (Figure 3). At this time, the patient was referred to Gynecology Oncology and Gastroenterology for further evaluation of recurrent ascites of unknown etiology.

She underwent a diagnostic laparoscopy notable for persistent diffuse ascites and fleshy-appearing peritoneal nodules. A nodule biopsy was sent for histopathologic evaluation and findings were consistent with malignant peritoneal mesothelioma, epithelioid subtype (Figure 4 and 5). Subsequent PET-CT was performed which illustrated peritoneal carcinomatosis (Figure 6).

The pathologic diagnosis of malignant peritoneal mesothelioma is challenging due to the variety of microscopic morphologies that mesothelial cells exhibit. Our diagnosis was made with several immunohistochemistry markers due to common cross-reactivity in different tissue types. Currently, a number of immunostains may be used to identify mesothelial

cells such as: AE1/AE3, CK5/6, Calretinin, WT1, D2-40, vimentin, and h-caldesmon. Due to cross-reactivities with adenocarcinoma cells, at least two markers are recommended to diagnose malignant peritoneal mesothelioma. In our presented case, the patient's neoplastic cells were immunoreactive for calretinin and CK5/6 (Figure 7), as well as AE1/AE3, WT-1, D2-40 while negative for MOC31, Ber-EP4, ER, Pax-8 (Figure 8), CEA and CD1. Collectively, these findings supported the diagnosis of DMPM.

The patient was immediately referred to a cancer center where she received multidisciplinary medical and surgical care. After thorough counseling on future fertility options, the patient declined oocyte or embryo cryopreservation and decided to proceed with ovarian suppression prior to treatment. She received the GnRH

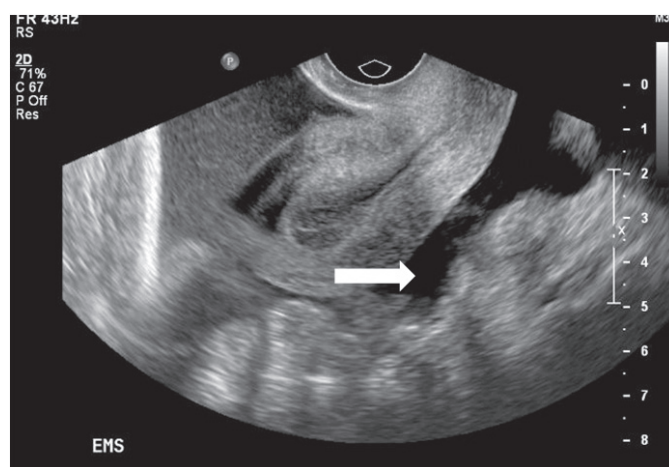


Figure 1: Transvaginal US showing arrow pointing to free fluid surrounding the uterus.

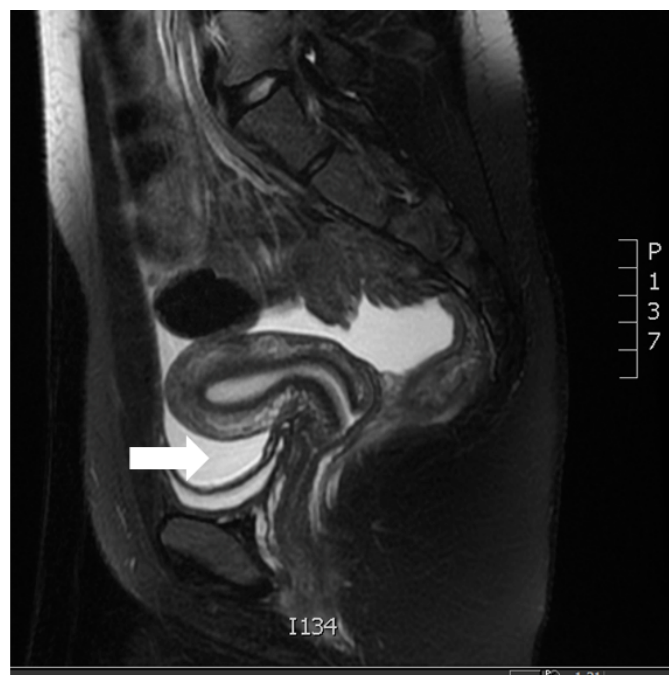


Figure 2: MRI image of the pelvis and abdomen with arrow pointing to ascitic fluid present.

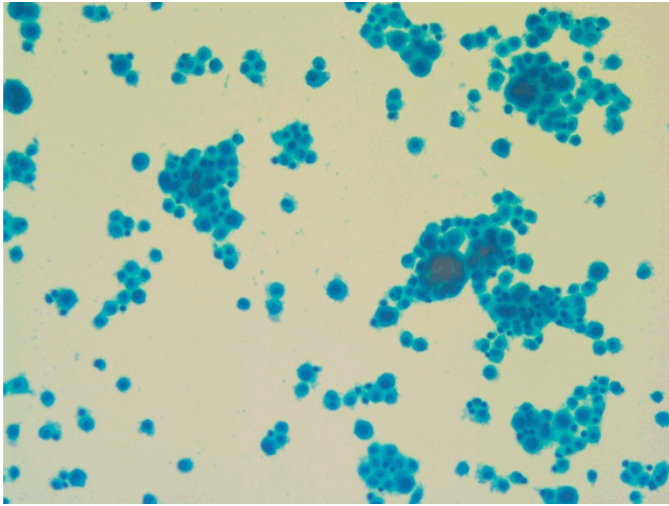


Figure 3: Cytologic preparation of peritoneal fluid showing a hypercellular specimen with large mesothelial cells present singly and in clusters (200x).

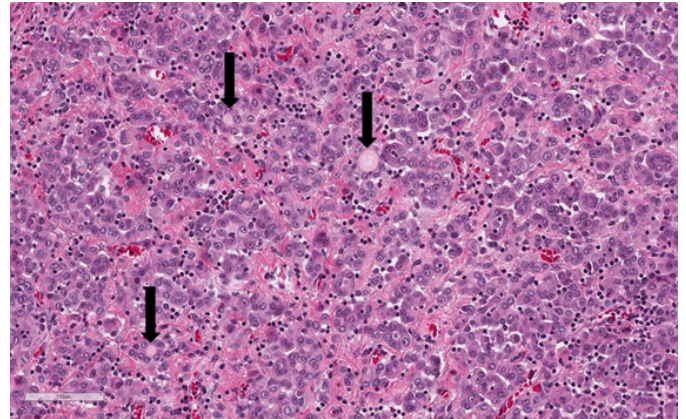


Figure 5: High power view demonstrates monotonous malignant mesothelial cells with abundant cytoplasm, pseudoglandular formations (arrows), and mild nuclear atypia with prominent nucleoli (200x).



Figure 4: Low power view of one of the peritoneal nodules.

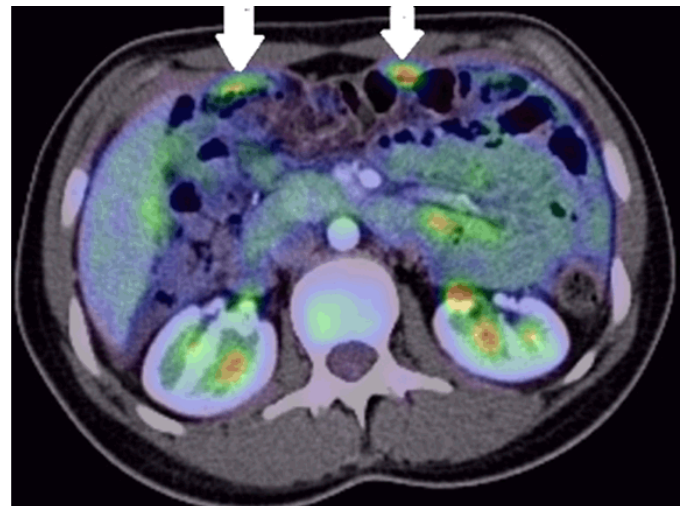


Figure 6: PET CT overlay of mesothelioma peritoneal nodules (arrows).

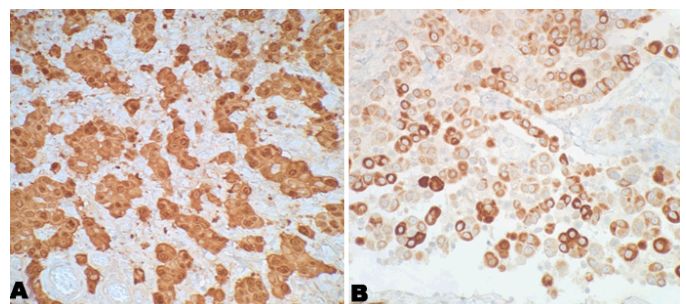


Figure 7: Immunohistochemistry slides are immunoreactive for Calretinin (A) and CK 5&6 (B) which are mesothelial cell markers.

agonist, Goserelin, 3.6 mg subcutaneously every month throughout the duration of her oncologic care. The patient's surgical oncologists performed cytoreductive surgery with the removal of epigastric and small bowel mesenteric implants, omentum, appendix, spleen, peritoneum of Morison's Pouch, and lymph nodes along the small bowel and transverse mesocolon. At the time of surgery, she was concurrently treated with hyperthermic intraoperative peritoneal Cisplatin chemotherapy (HIPEC).

After surgical recovery, she completed adjuvant chemotherapy with carboplatin (AUC 5) 580 mg and Premetrexed 500 mg/m² (870 mg) for six 21-day cycles. All treatment was completed within nine months. A follow-up diagnostic laparoscopy and esophagogastroduodenoscopy (EGD) was performed. Surgical findings demonstrated no persistent or recurrent

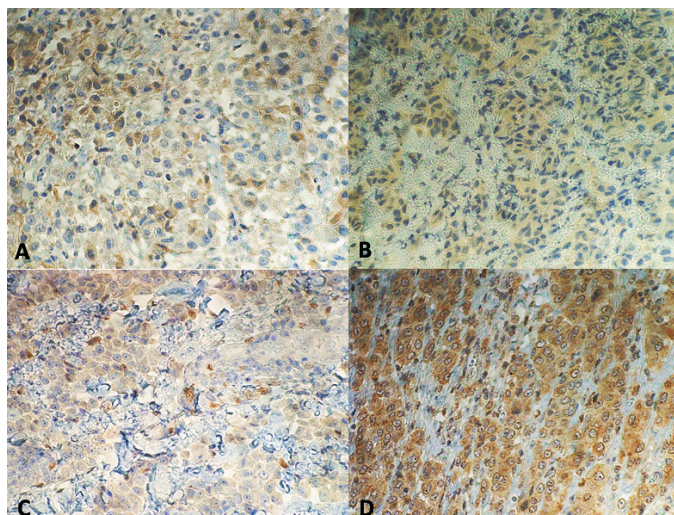


Figure 8: Immunohistochemistry slides are non-reactive for BER-EPA4 (A), MOC-31(B), ER (C), PAX-8 (D).

pelvic or abdominal tumor nodules or lymphadenopathy. The stomach, duodenum, and examined jejunum (intubated 100 cm from mouth) were normal. The patient was followed by her oncology care team with CT imaging studies at three month intervals. Almost 18 months after completion of chemotherapy, the patient reported spontaneous return of menses. After two years of uneventful surveillance with no evidence of recurrent disease, she was released to pursue fertility care.

Prior to her diagnosis of malignant peritoneal mesothelioma, the patient's antimullerian hormone (AMH) value was notably low-normal at 1.5 ng/ml. After treatment, the patient was presumed to have significant diminished ovarian reserve with an AMH of 0.26 ng/ml. She underwent an in vitro fertilization (IVF) stimulation cycle with a GnRH-agonist microdose flare protocol. Maximum doses of gonadotropin stimulation were 300 IU daily of follitropin-beta and 225 IU daily of menotropin. Her peak estradiol value was 874 pg/mL and oocyte retrieval yielded five mature oocytes. Intracytoplasmic sperm injection was performed leading to two successfully fertilized zygotes. The patient underwent an uneventful day three embryo transfer of two high-quality cleavage embryos. Twelve days later a serum bHCG value returned positive at 168.7 mIU/ml with an appropriate 48-hour interval rise to 433.0 mIU/ml. At seven weeks gestation, ultrasound imaging confirmed a single, viable intrauterine pregnancy with positive fetal cardiac activity. Her pregnancy continued, uneventfully, to 38 weeks 6 days before delivering a healthy female infant weighing 6 pounds 12 ounces.

DISCUSSION

Historically, DMPM has been regarded as a fatal, terminal disease. Cure rates were previously dismal with an overall median survival of approximately one

year [4]. Upon presentation, DMPM was often treated with a combination of systemic chemotherapy, palliative surgery, and whole abdomen irradiation. Recent advances in treatment and management strategies have improved overall survival rates with a remarkable prolongation in median survival of patients treated with CRS and HIPEC to approximately 50% at five years [5–7]. Patients surviving greater than seven years are deemed to be cured with rates reaching as high as 43 % in recent studies [3].

An Italian study by Baratti and colleagues sought to identify specific prognostic factors for patients afflicted with DMPM. In this study, a prospective database was utilized to identify 108 patients with DMPM who underwent cytoreductive surgery and HIPEC. The most notable favorable immunohistologic prognostic factors for survival were immunoreactivity for calretinin, cytokeratin 5/6, Wilms tumour-1 (WT1), and podoplanin (D2-40) [3]. Our patient's histopathology revealed reactivity to all four of these positive prognostic factors.

To our knowledge, we report the first case of a successful IVF-achieved live birth following CRS, HIPEC and adjuvant chemotherapy treatment for DMPM in a young female with peritoneal mesothelioma. Various key words (e.g. diffuse malignant peritoneal mesothelioma, IVF pregnancy after DMPM, Pregnancy after CRS and HIPEC) were utilized to search for related articles using OVID and PUBMED online data search engines. We discovered a published case series describing nine patients with pregnancies following a diagnosis of peritoneal malignancy [8]. Two of the patients conceived after their diagnosis of malignancy, but prior to CRS and HIPEC therapy. Both required advanced reproductive technologies to achieve pregnancy; one patient underwent IVF and embryo cryopreservation with subsequent use of a gestational surrogate to carry a resultant twin gestation. The remaining seven patients in this series conceived spontaneously within six years following treatment with CRS and HIPEC. Unlike our patient, none of the remaining seven patients described in this case series received postoperative systemic chemotherapy. Additionally, the authors of this series did not comment on any use of ovarian suppression during treatment.

A separate study discovered in our literature search described the case of an IVF-achieved pregnancy following CRS and HIPEC for pseudomyxoma peritonei. In contrast to the care provided to our patient, the HIPEC therapy reported in this study encompassed only Mitomycin C and the post-surgical care did not include adjuvant systemic chemotherapy. Again, the authors did not remark upon intentional fertility preservation by means of ovarian suppression [9].

In light of increased long term survival and cure, future fertility should be considered for reproductive-aged women with DMPM prior to initiation of CRS and HIPEC treatment [10]. Options for future fertility are dependent upon the acuity of the disease and timely access to advanced reproductive technologies, along with the cost of oocyte and embryo cryopreservation. It

is unknown what level of benefit, if any, GnRH-agonist therapy for ovarian suppression provides during CRS and HIPEC therapy. However, as our case report reveals, ovarian suppression with a GnRH-agonist may be an advantageous option for those unable or unwilling to pursue alternatives such as pre-chemotherapy oocyte or embryo cryopreservation.

CONCLUSION

Patients diagnosed with DMPM of reproductive age should have a multidisciplinary team approach for counseling of future fertility desires. Specialists in fertility preservation may be able to offer oocyte or embryo cryopreservation prior to initiating CRS and HIPEC treatment. However, the access to and costs of assisted reproductive technologies may be an important limiting factor in joint decision making. Ovarian suppression with a GnRH agonist holds promise as a potential suitable alternative option for women who are unwilling or unable to pursue pre-treatment oocyte or embryo cryopreservation.

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Ashley Ornoff MD, Department of Pathology, San Antonio Military Medical Center, Fort Sam Houston, Texas

Author Contributions

Viviana de Assis – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Jaye Adams – Substantial contributions to conception and design, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Johanna Hollweg Marowske – Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Allyson Cochet – Substantial contributions to conception and design, Drafting the article, Critical revision of the article, Final approval of the version to be published

Doug Walton – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Final approval of the version to be published

Rhiana Saunders – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor of Submission

The corresponding author is the guarantor of submission.

Source of Support

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Consent Statement

Written informed consent was obtained from the patient for publication of this case report.

Conflict of Interest

Authors declare no conflict of interest.

Data Availability

All relevant data are within the paper and its Supporting Information files.

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