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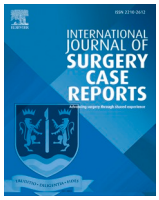

Case report

Metastatic ovarian carcinosarcoma in a patient undergoing in-vitro fertilization: A case report

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ABSTRACT

Introduction and importance: Ovarian carcinosarcomas (OCS) are highly aggressive tumors containing both carcinomatous and sarcomatous elements. Patients are typically older postmenopausal women who present with advanced disease, however rarely young women can be affected.

Case presentation: A 41-year-old woman undergoing fertility treatment was found to have a new 9–10 cm pelvic mass on routine transvaginal ultrasound (TVUS) 16 days after embryo transfer. Diagnostic laparoscopy revealed a mass in the posterior cul-de-sac that was surgically excised and sent to pathology for evaluation. Pathology was consistent with carcinosarcoma of gynecologic origin. Further work-up revealed advanced disease with apparent rapid progression. Patient underwent interval debulking surgery after four cycles of neoadjuvant chemotherapy with carboplatin and paclitaxel with final pathology consistent with primary ovarian carcinosarcoma and complete gross resection of disease.

Clinical discussion: In the setting of advanced disease neoadjuvant chemotherapy with a platinum-based chemotherapy regimen followed by cytoreductive surgery is a standard approach to treatment of OCS. Given the rarity of disease, most data regarding treatment has been extrapolated from other forms of epithelial ovarian cancer. Specific risk factors for disease development of OCS including the long-term effects of assisted reproductive technology remain understudied.

Conclusion: While OCS are rare highly aggressive biphasic tumors that primarily affect older postmenopausal woman, we present a unique case of OCS incidentally found in a young woman undergoing fertility treatment via in-vitro fertilization.

1. Introduction

Carcinosarcomas are highly aggressive biphasic tumors consisting of both carcinomatous and sarcomatous elements. Also known as malignant mixed Müllerian tumors (MMMT), these neoplasms are exceedingly rare and account for only 1–4 % of ovarian cancers [1]. Ovarian carcinosarcoma (OCS) primarily affects older postmenopausal women with a median age of onset between 60 and 70 years old.

This highly aggressive form of ovarian cancer typically carries a poorer prognosis than more common epithelial ovarian cancers [2]. Approximately 10 % of ovarian cancers are non-epithelial type and include germ cell tumors, sex cord-stromal tumors, as well as rarer histologic sub-types such as small cell carcinomas and carcinosarcomas. Among the non-epithelial ovarian cancers, germ cell tumors are diagnosed principally in the first three decades of life, whereas sex-cord stromal tumors occur in more different age groups, regardless both tumor types have favorable outcomes. In contrast, small cell carcinomas and carcinosarcomas have extremely poor prognosis and aggressive biological behavior [3].

Patients with OCS often present with symptoms of advanced disease including pelvic pain, bloating, abdominal distension, or early satiety. Most patients present with an International Federation of Gynecology and Obstetrics (FIGO) stage of III-IV [1,4].

Limited prospective studies exist regarding the management of OCS given the rare and aggressive nature of the condition. The majority of data regarding treatment of OCS has been extrapolated from retrospective studies often with a relatively small sample size [1]. The mainstay treatment includes optimal cytoreductive surgery in addition to adjuvant platinum-based chemotherapy possibly in combination with paclitaxel or ifosamide [5].

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We report a unique case of ovarian carcinosarcoma that was diagnosed during surveillance following in-vitro fertilization. This case has been reported in line with the SCARE criteria [6].

2. Presentation of case

The patient is a 41-year-old, gravida 2, para 0, white female who presented for work-up of a newly discovered pelvic mass. The patient was undergoing fertility treatment via in-vitro fertilization and had undergone an uncomplicated embryo transfer 16 days prior to presentation. Following the embryo transfer the patient had close surveillance with her reproductive endocrinologist with a normal beta human chorionic gonadotropin (bHCG) trend. An ultrasound performed in the outpatient setting on post-transfer day 16 revealed a new 9 cm left pelvic mass that was not present on the multiple prior serial ultrasounds performed at time of ovarian stimulation, egg retrieval, and embryo transfer.

Transvaginal ultrasound demonstrated a large echogenic mass measuring up to 9 cm extending from the midline of the pelvis toward the left adnexa (Fig. 1). Magnetic resonance imaging (MRI) demonstrated a 9 cm extrauterine mass centered in the posterior cul-de-sac of the pelvis displacing the uterus anteriorly (Fig. 2). The mass had signal characteristics consistent with a solid lesion. While findings were not typical of an ectopic pregnancy, in the setting of recent embryo transfer procedure this was considered as a differential diagnosis. bHCG had been closely followed and appropriately risen from 12.96 mIU/ml (day 9 post transfer) to 104.8 mIU/ml (day 13) to 287.9 mIU/ml (day 16). A normal intrauterine pregnancy with unrelated pelvic mass was also considered given appropriate rise in serum bHCG since embryo transfer.

Diagnostic laparoscopy performed by a gynecologic oncologist revealed approximately 100 ml of hemoperitoneum upon entry with a 10 cm friable hemorrhagic pelvic mass in the posterior cul-de-sac with a thick stalk (Fig. 3). The mass arose from the rectovaginal septum. Additional small clusters of 1-2 mm soft pink superficial lesions were present on the left and right anterior cul-de-sac peritoneum as well as the right uterosacral ligament. No adhesions were present. A pelvic survey revealed a grossly normal appearing uterus, bilateral fallopian tubes, and bilateral ovaries. The upper abdomen appeared normal on survey. The surgical procedure was limited to resection of the pelvic mass as well as peritoneal biopsies which were subsequently sent for pathologic evaluation.

Pathologic evaluation of the pelvic mass revealed a biphasic tumor showing high-grade carcinoma and sarcoma elements. The pelvic biopsy showed additional sarcoma along with focal endometriosis. Immunohistochemical staining was positive for paired box protein 8 (PAX8) supporting a tumor of gynecological origin. Post-operative abdominal and pelvic computed tomography (CT) was performed two weeks post-operatively and showed no obvious tumor recurrence or evidence of metastatic disease.

The patient re-presented to the emergency department 9 days following the CT scan with a worsening subjective bloating sensation. Repeat abdominal and pelvic CT showed peritoneal carcinomatosis and large volume ascites. Given rapid disease progression, recommendation was made for neoadjuvant chemotherapy (NACT) with carboplatin and paclitaxel every 3 weeks for 4 cycles.

Following the four cycles of NACT, interval imaging was performed. Abdominal and pelvic CT showed significantly decreased peritoneal carcinomatosis with resolved ascites with decreased size and heterogeneity of bilateral adnexa. Patient underwent total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, and optimal debulking with excision of rectal and pelvic implants with complete gross resection. Final pathology was consistent with ovarian carcinosarcoma involving the right fallopian tube and surface of the right ovary.

She underwent an additional two cycles of carboplatin and paclitaxel post-operatively with the addition of bevacizumab in cycle 6. The patient is currently on bevacizumab maintenance therapy with the most recent interval CT showing no evidence of disease.

3. Discussion

Carcinosarcoma is a rare neoplasm that has been found in multiple organ systems including the uterus, ovary, kidney, biliary tree, breast,

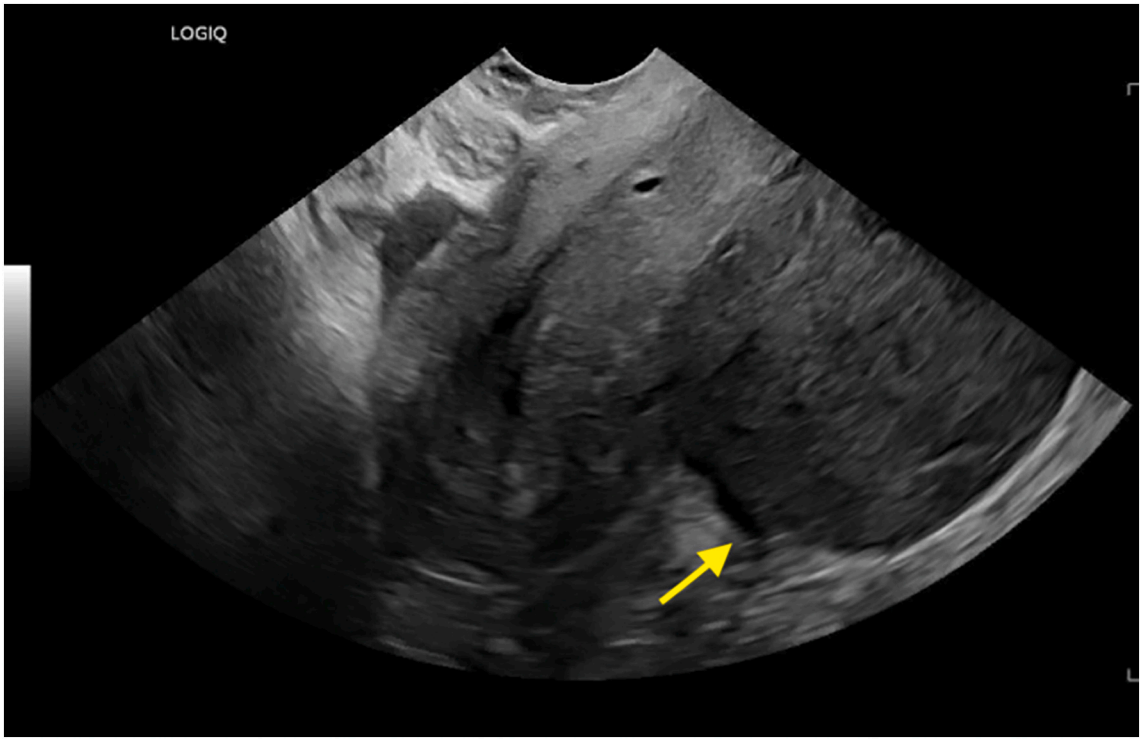

Fig. 1. Transvaginal ultrasound sagittal view of the uterus and posterior-cul-de sac demonstrating 8.9 cm echogenic mass arising from the pelvic midline.

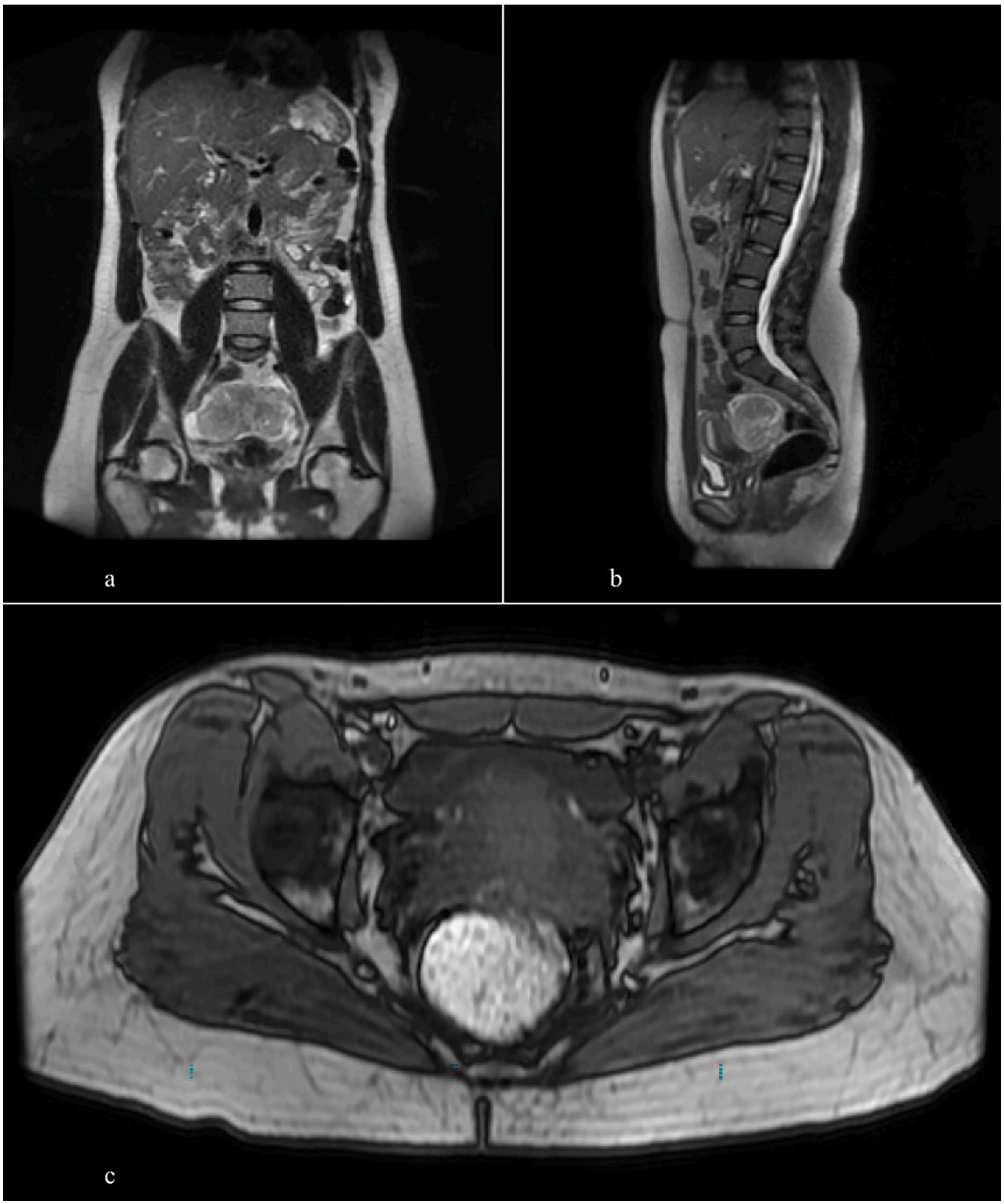

Fig. 2. Magnetic resonance imaging (MRI) demonstrating a 9 cm extrauterine T2 hyperintense, T1 hypointense, diffusion restricting solid appearing mass centered in the posterior cul-de-sac of the pelvis A: Coronal view B: Sagittal view C: Axial view.

lung, thyroid, and liver [7]. These tumors contain both a carcinomatous and sarcomatous element. Ovarian carcinosarcoma (OCS) specifically is a rare tumor accounting for less than 4 % of ovarian cancers. As a result of the sarcomatous element these tumors can be extremely aggressive and resistant to many treatment options. Prognosis is overall poor with a high rate of recurrence and a median overall survival of about 21 months [8].

Multiple theories have been hypothesized to explain the biphasic nature of these tumors including the collision theory, combination theory, and conversion theory. The collision theory suggests that the carcinomatous element and sarcomatous elements each arise independently from different cell lines. The combination theory hypothesizes

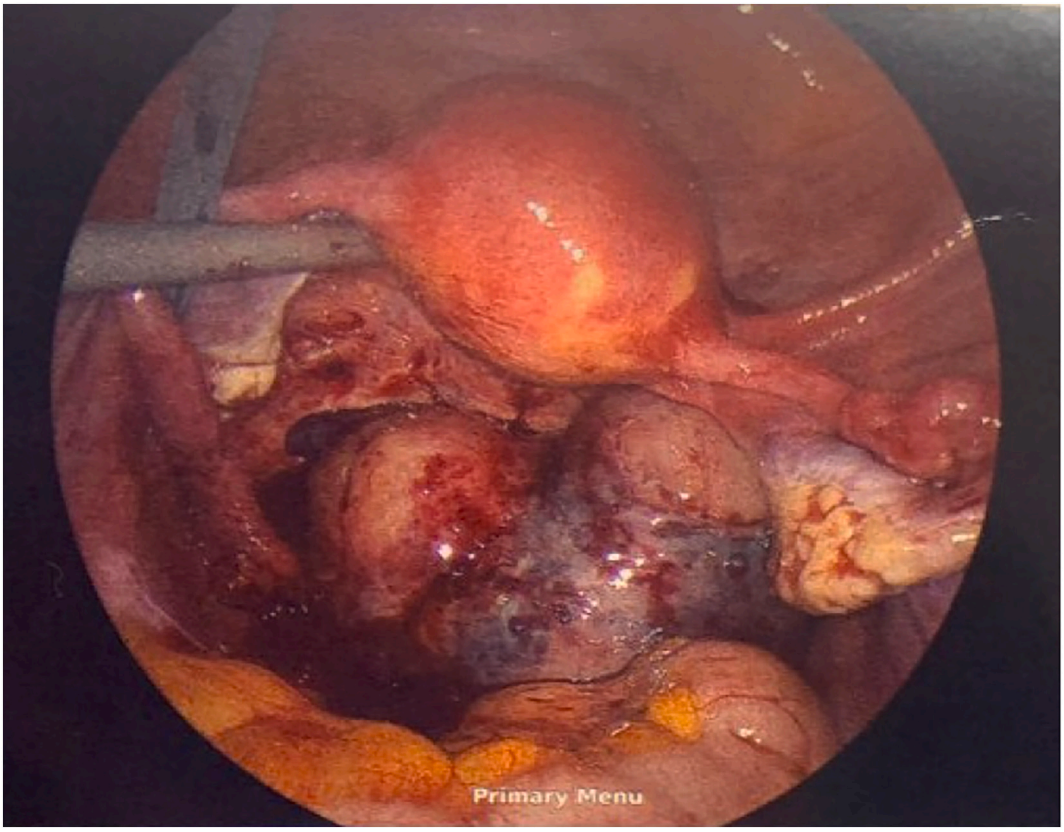

Fig. 3. 10 cm friable hemorrhagic pelvic mass in the posterior cul de sac with a thick stalk arising from the rectovaginal septum.

that both the components derive from a single progenitor cell. Finally, the conversion theory suggests that a single epithelial component undergoes metaplastic differentiation to form the sarcomatous element [7,9].

As a result of the rarity of the disease few prospective studies exist, and treatments largely have been extrapolated from those of other forms of epithelial ovarian cancer. Cytoreductive surgery remains the preferred treatment. Platinum-based chemotherapy in combination with paclitaxel or ifosfamide also plays an important adjuvant role in treatment [5,10,11]. In more advanced cases, neoadjuvant chemotherapy can be considered to ensure optimal debulking [12].

This case demonstrates an unusual presentation of ovarian carcinosarcoma in a young pre-menopausal woman undergoing fertility treatment. Given the unusual presentation of a discrete pelvic mass with grossly normal appearing uterus, fallopian tubes and ovaries, the tumor origin remained unknown until initial pathology suggested gynecologic origin. Immunostaining was positive for PAX8, a transcription factor that plays an important role in the development of the Müllerian duct. Expression of PAX8 helped identify the origin of this tumor and guided treatment. Additionally, initial pathology demonstrated focal endometriosis further suggesting gynecologic origin [13]. Malignancies, including OCS, arising from endometriosis have been described in the literature. Approximately 80 % of malignancies associated with endometriosis are identified in the ovary [14,15]. An underlying diagnosis of endometriosis may explain an increased risk of endometroid or clear cell ovarian cancer in such a young patient.

An additional consideration in this case is the recent fertility treatment. The long-term effects of assisted reproductive technology (ART) on ovarian cancer risk remains an interesting focus of research. A recent large cohort study showed an increased risk of ovarian cancers in patients undergoing ART when compared with the general population, however this risk may be attributed to population characteristics such as nulliparity rather than ART itself [16]. Given the current body of literature on ART and ovarian cancer risk it is difficult to say whether the development of this tumor can be linked to hormone stimulation. Another plausible explanation is that this was an incidental finding of de-novo tumor during the close monitoring of ART.

While unusual to find the "primary" ovarian lesion extragenital, one possible hypothesis for the location of the original identified mass is that the initial tumor from the ovary was seeded in the posterior cul-de-sac at the time of egg retrieval during fertility treatment. It is also possible that the carcinosarcoma spontaneously developed from an endometriosis implant with ovarian remnant in the posterior cul-de-sac of the pelvis.

This case truly highlights the aggressive nature of this neoplasm as we have multiple imaging studies performed over the span of only a few weeks that show the development of an extragenital mass, rapid accumulation of ascites and peritoneal carcinomatosis. Despite rapid progression, the patient showed optimal response to neoadjuvant chemotherapy and was able to undergo interval debulking surgery with complete gross resection of disease.

Multiple phase II trials are ongoing to evaluate chemotherapy regimens as well as, novel and combination immunotherapies. Molecular targets remain broad including poly ADP ribose polymerase (PARP), programmed cell death protein-1 (PD-1), vascular endometrial growth factor (VEGF), and Dickkopf-1 (DKK1) antibody. While the rate of BRCA1 and BRCA2 mutations in ovarian carcinosarcomas is difficult to ascertain, genomic sequencing in some studies has demonstrated loss of function mutations in homologous recombination genes, which is the rationale for use of PARP inhibition even in OCS [17]. Still, the optimal treatment for ovarian carcinosarcoma remains unclear and further research is needed to optimize treatment for these patients.

4. Conclusion

In conclusion this report adds to the growing body of literature about ovarian carcinosarcoma and its highly aggressive and unusual nature.

This case demonstrates that OCS is not limited to older post-menopausal woman and can affect younger pre-menopausal woman without additional risk factors. While little data exists for the optimal treatment method, our patient responded to NACT and interval surgical debulking. Furthermore, this case may potentially demonstrate a link between ART and malignancy risk. More studies are necessary to continue to understand ovarian carcinosarcoma to improve treatments and long-term outcomes.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of written consent is available for review by the Editor-in-Chief of this journal on request.

Ethical approval

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Research registration

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Guarantor

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CRediT authorship contribution statement

Matthew Flint MD: Conceptualization, Investigation, Writing - Original draft preparation. Jessica Velasquez MD: Investigation, Writing – Original draft preparation. Caitlin Carr MD: Visualization, Writing – Review and Editing. Valentin Kolev MD: Supervision, Writing – Review and Editing. Konstantin Zakashansky MD: Supervision, Writing – Review and Editing.

Declaration of competing interest

The authors declare that there are no conflicts of interest.

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