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Case report

Invasive endometrial adenocarcinoma and missed abortion: A case report

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ABSTRACT

Background: Endometrial cancer is the most common gynecologic cancer in the United States; however, reports of endometrial cancer diagnosed in the setting of intrauterine gestation are rare.
Case: We describe the case of a clinical stage IA grade 1 endometrioid endometrial adenocarcinoma diagnosed at the time of D&C performed for missed abortion in a gravida 1 para 0 female with no identifiable risk factors. Fertility-sparing treatment, with combined oral megestrol acetate and levonorgestrel intrauterine system, was used to manage this incidentally-diagnosed carcinoma with endometrial sampling every 3 months.

1. Introduction

Endometrial cancer is the most common gynecologic malignancy and the 10th most common cancer amongst women with an estimated 61,880 new cases and 12,160 cancer related deaths in 2019 (Howlader et al., 2018). The median age of endometrial cancer diagnosis is 63 and more than 75% of cases are diagnosed after age 55. Only approximately 7% of endometrial cancers are diagnosed in reproductive age women under the age of 45. Exceedingly rare is the diagnosis of endometrial cancer with concurrent pregnancy and to the best of our knowledge, only few cases have been reported in the literature.

In contrast to cervical cancer screening, endometrial biopsy is not routinely performed to screen for endometrial cancer in asymptomatic patients. Furthermore, with only 7% of endometrial cancers diagnosed in women of reproductive age, endometrial sampling is of low yield in this patient population. Lastly, endometrial biopsy is contraindicated in pregnancy, as it risks disrupting development of the fetoplacental unit. For these reasons, clinical scenarios resulting in synchronous intrauterine gestation and endometrial cancer are rare. Most commonly, these concurrent diagnoses are made at the time of dilation and curettage (D&C) performed for incomplete or missed abortion (Zhou et al., 2015). Here, we report a case of endometrial adenocarcinoma diagnosed at the time of D&C for a spontaneously conceived pregnancy of unknown location and an inappropriately rising β-hCG in a patient with no risk factors for endometrial cancer.

2. Case report

A 37 year old gravida 1 para 0 with a planned, spontaneously conceived, and desired pregnancy presented for routine obstetrical care at approximately 8 weeks gestational age (by last menstrual period). At her initial prenatal visit, she endorsed heavy vaginal bleeding in the preceding days. Her past medical and gynecologic history were otherwise unremarkable. She denied a history of alcohol, tobacco, and illicit drug use. She does not have any relevant oncologic family history. Physical exam revealed a well appearing Caucasian female, body mass index 20. Pelvic exam demonstrated a 6 week size uterus and blood in the vaginal vault. An ultrasound was performed revealing no intra-uterine or extra-uterine pregnancy but the presence of blood in the lower uterine segment. Quantitative β-hCG was 37,221 mIU/mL and, 2 days later, was 44,934 mIU/mL. A repeat ultrasound again did not identify an intra-uterine or extra-uterine gestational sac, embryo, or yolk sac. However, the ultrasound did reveal a 3 cm echogenic cystic mass in the endometrial cavity with vascular flow from the anterior myometrium. In the presence of an abnormally rising β-hCG with a pregnancy of unknown location, the decision was made to proceed with dilation & curettage (D&C). She underwent an uncomplicated D&C and pathologic frozen section confirmed the presence of villi. Histology revealed well differentiated endometrioid adenocarcinoma and atypical hyperplasia immediately adjacent to concurrent products of conception consistent with missed abortion (Fig. 1). The endometrium demonstrated a spectrum of epithelial changes, ranging from hypersecretory endometrium to atypical complex hyperplasia to well differentiated

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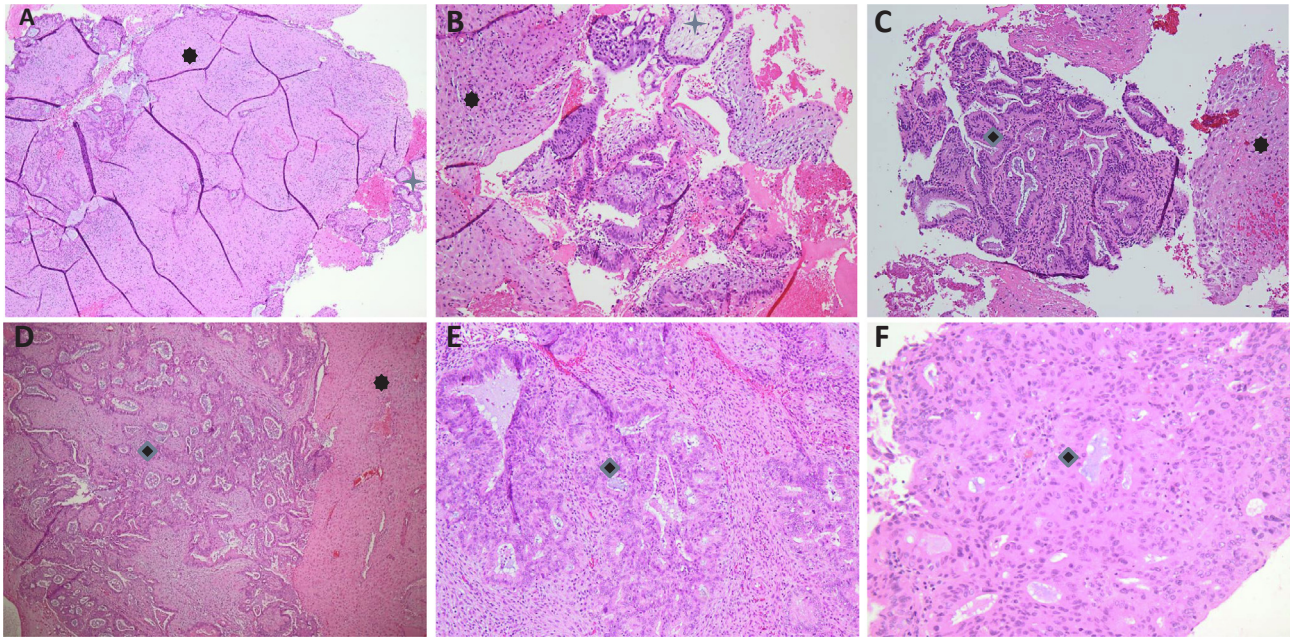

Fig. 1. Microscopic examinations of Products of Conception on Hematoxylin and Eosin Stains A, D: Low power view (4x); B, C, E: Medium power view (10x); F: High power view (20x). Decidua (✹), Chorionic villi (+), endometrial hyperplasia or carcinoma (◆).

adenocarcinoma (back-to-back glands without intervening stroma). Degenerating immature chorionic villi, necrotic decidua, and hemorrhage were identified in line with the patient's history of missed abortion. There was no histologic evidence of gestational trophoblastic disease. Immunohistochemically, the carcinoma retained nuclear expression of four mismatch repair proteins (MLH-1, MSH-2, MSH-6, and PMS-2).

Postoperatively, the β-hCG was serially trended to 8 mIU/mL. The patient was referred for gynecologic oncology consultation. A pelvic MRI was performed, demonstrating a 1.1 × 1.3 cm heterogeneous mass along the anterior wall of the uterus with some junctional zone invasion but no myometrial invasion (Fig. 2). The patient was counseled regarding management options including definitive surgical staging and hormonal management. As the patient desired future fertility, she elected for conservative management with levonorgestrel IUD and megestrol acetate 160 mg/day with planned endometrial sampling every 3 months. At the 3 month interval, D&C with hysteroscopy was performed; hysteroscopy was significant for a papillary lesion on the anterior aspect of the endometrium (Fig. 3A). Pathology demonstrated a few foci of complex atypical hyperplasia and endometrioid adenocarcinoma, FIGO grade 1, in a background of inactive endometrium with progestin effect, representing areas of partial response and areas of persistent disease. Hormonal management was continued. At 6 months, hysteroscopic evaluation of the endometrium demonstrated a persistent papillary lesion along the anterior uterine body, which was resected under direct visualization using the MyoSure® tissue removal system. Pathology demonstrated persistent grade 1 endometrioid adenocarcinoma and hormonal therapy was continued. At 9 months, endometrial

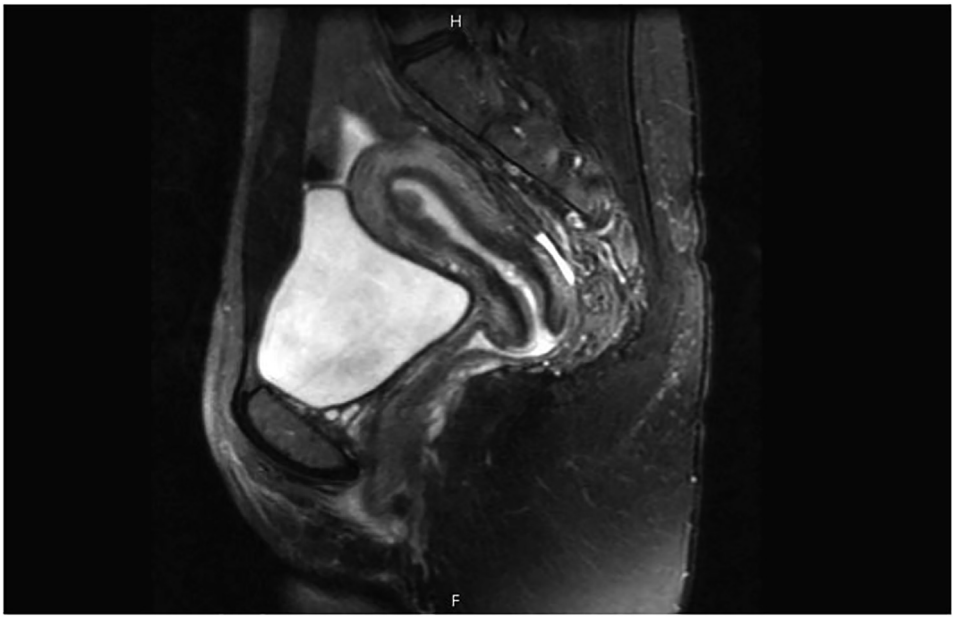

Fig. 2. Pelvic MRI demonstrating 1.1 × 1.3 cm mass along the anterior uterine wall without evidence of myometrial invasion.

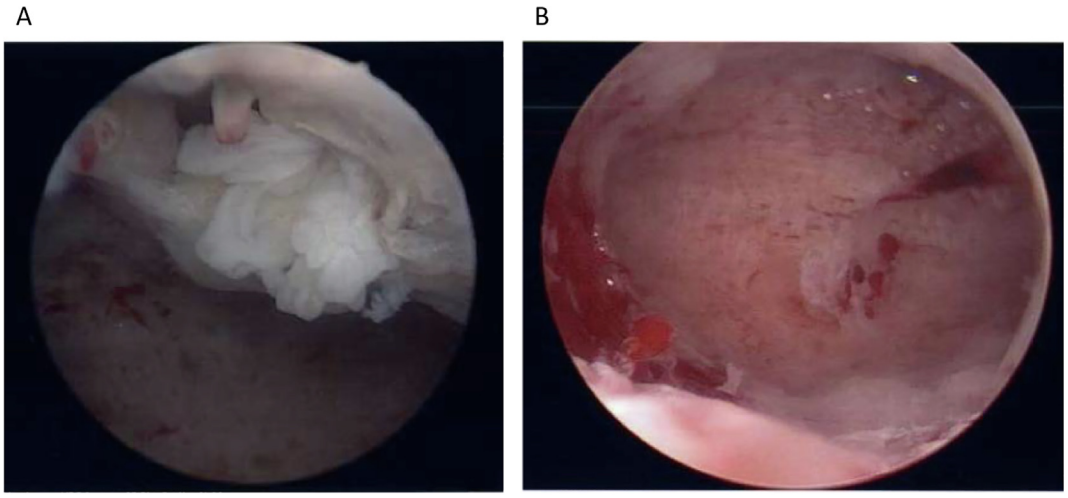

Fig. 3. A: Hysteroscopy after 3 months of combined hormonal therapy demonstrated persistent papillary lesion of anterior uterine wall. B: Hysteroscopy after 9 months of combined hormonal therapy demonstrated resolution of malignancy.

sampling demonstrated no evidence of residual malignancy (Fig. 3B). Genetic evaluation was performed and was negative for pathologic mutations, including PTEN. She was continued on hormonal therapy for a 3 months following resolution of malignancy and greater than 1 year since her diagnosis. She is currently under the care of reproductive endocrinology for in vitro fertilization. Definitive hysterectomy will be considered at the completion of childbearing.

3. Discussion

First trimester pregnancy with concurrent endometrial cancer is a rare occurrence and, to the best our knowledge, has been reported in the literature only a few times, with most cases associated with spontaneous abortion (Zhou et al., 2015). Of reported cases, nearly 50% were diagnosed during the first trimester and an additional 33% were diagnosed postpartum. Interestingly, many of these patients did not possess the typical risk factors for endometrial adenocarcinoma (Vaccarello et al., 1999). Risk factors associated with endometrial cancer include prolonged unopposed estrogen exposure, as seen in obesity and polycystic ovarian syndrome, genetic syndromes, such as Lynch and Cowden Syndromes, and older age. The patient presented here possesses none of these risk factors: she was 37 years old at the time of presentation, BMI 20, negative panel testing for pathogenic genetic mutation.

Additionally, elevated levels of progesterone, as seen in pregnancy, are typically thought to be protective of the endometrium. Risberg et al. have demonstrated that areas of the endometrium that have undergone malignant transformation may be resistant to the protective effects of progesterone, thus allowing for the development of cancer (Risberg et al., 1983). Interestingly, treatment considerations of reproductive aged women with endometrial cancer often include the option of medical management with progestin therapies, which mimics the endogenous progesterone rich state of pregnancy.

The patient we present is young and desires future fertility. To our knowledge, this is the first report of a patient with endometrial cancer diagnosed in pregnancy being treated with a combination of the levonorgestrel IUD and megestrol acetate. A large systematic review including 391 patients described the utilization of hormonal therapies for complex atypical hyperplasia and grade 1 endometrial adenocarcinoma. Durable response rates are reported to be 48.2% for grade 1 endometrioid adenocarcinoma with 34.8% achieving pregnancy after treatment. Of those patients with endometrial cancer, 74.6% had an initial complete response at a median time of 6 months but 35.4% eventually recurred at a median time of 24 months. One quarter of patients had persistent or progressive disease, when treated with a variety of progestin regimens, including medroxyprogesterone acetate, megestrol acetate, levonorgestrel intrauterine system, intramuscular 17-hydroxyprogesterone, oral contraceptive pills, norethisterone, dihydrogesterone and natural progesterone (Gunderson et al., 2012). Notably, others have reported on conservatively managed endometrioid adenocarcinoma that rapidly progressed after successful term pregnancies (Ferrandina et al., 2005). Kim et al. described utilization of combined oral medroxyprogesterone acetate and levonorgestrel intrauterine system in 16 patients; 87.5% of patients had a complete remission, defined as no evidence of hyperplasia or cancerous lesion on biopsy (Kim et al., 2013). Given the potential for persistent or progressive disease, definitive hysterectomy should be strongly considered after pregnancy.

Consent

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

Author contribution

All co-authors have seen and agree with the contents of this manuscript. Each author played a role in the concept design, analysis, drafting and revisions of this manuscript.

Declaration of Competing Interest

The authors have no personal or financial affiliations to disclose.

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