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Estrogen receptor-positive adenocarcinoma of the cervix presenting during pregnancy: Two case reports and review of the literature

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ABSTRACT

The incidence of adenocarcinoma of the cervix in pregnancy is exceptionally rare, and thus there is no consensus on its management. Here, we report two cases of adenocarcinoma of the cervix diagnosed in the context of pregnancy. In our first case, a patient referred to colposcopy for atypical glandular cells of undetermined significance was subsequently diagnosed with well differentiated endocervical adenocarcinoma on cone biopsy. Just prior to the cone biopsy, she was incidentally found to have a first trimester pregnancy loss. The patient subsequently underwent a radical hysterectomy and bilateral sentinel lymph node dissection. Final pathology revealed a stage 1B1 (FIGO 2009) well differentiated adenocarcinoma of the cervix. Interestingly, the tumour was positive for estrogen receptor, which is unusual for cervical adenocarcinoma.

In our second case, a patient presented with a pedunculated, exophytic cervical neoplasm at 31 weeks GA with self-limiting antepartum hemorrhage. The primary lesion measured 52 mm in diameter on MRI and was amputated at the base during the patient's elective repeat cesarean section. Final pathology revealed a stage IB2 (FIGO 2009) mucinous adenocarcinoma of the cervix. The patient subsequently underwent a radical hysterectomy and bilateral pelvic lymph node dissection 17 weeks after initial presentation. The depth of invasion was 2.2 mm, restricted to the inner third of the cervical wall, and there was no lymphovascular space invasion in the surgical specimen. Surgical margins, parametria, and lymph nodes were all negative for adenocarcinoma. This tumour was also found to be estrogen receptor/progesterone receptor (ER/PR) positive, again unusual for cervical adenocarcinoma. P16 was strongly positive and HPV DNA studies were also positive for human papilloma virus 18. The patient received adjuvant external beam radiotherapy to the pelvis and currently remains in remission.

1. Introduction

In North America, the median age of cervical cancer diagnosis is 47 years (Small et al., 2017). In the United States, over 40% of cervical cancer diagnoses occur in women of reproductive age (Hunter et al., 2008). Among these, 1–3% are diagnosed in the peripartum period (Bigelow et al., 2017) It has been estimated that 1.5–12 of every 100,000 pregnancies are complicated by invasive cervical cancer (Hunter et al., 2008). There is still no universal consensus in the management of cervical cancer diagnosed during pregnancy. While several clinical practice guidelines have examined the evidence on treatment of cervical malignancies during pregnancy, taking into consideration factors such as gestational age, disease stage, histology, and patient personal preference, (Han et al., 2013), the majority of cases are managed based on

List of abbreviations: CT, Computed Tomography; DFS, disease-free survival; EBRT, External Beam RadioTherapy; ER, Estrogen Receptor; GA, Gestational Age; HPVA, Human PapillomaVirus-Associated; IECC, International Endocervical Adenocarcinoma Criteria and Classification; IHC, Immuno-Histo-Chemistery; LVSI, LymphoVascular Space Invasion; MRI, Magnetic Resonance Imaging; NOS, Not Otherwise Specified; OS, Overall Survival; PFS, Progression Free Survival; PR, Progesterone Receptor; SCC, Squamous Cell Carcinoma.

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consensus after presentation at multi-disciplinary cancer case conferences. The majority of available evidence applies mainly to cases of squamous cell carcinoma (SCC) histology, since adenocarcinoma accounts for only 20–25% of all cervical malignancies (Bonin et al., 2019). Of note, under the 2017 International Endocervical Adenocarcinoma Criteria and Classification (IECC) system, mucinous adenocarcinoma is considered a subtype of Human Papillomavirus-Associated (HPVA) endocervical adenocarcinoma.

In this report we describe two cases of adenocarcinoma of the cervix diagnosed during pregnancy. The first case involves a stage 1B1 (FIGO 2009) adenocarcinoma of the cervix diagnosed following an early pregnancy loss, initially identified following cone biopsy of the cervix and subsequently treated with radical hysterectomy. The second case includes a stage IB2 (FIGO 2009) mucinous adenocarcinoma of the cervix diagnosed at the time of term delivery with subsequent radical hysterectomy and adjuvant pelvic radiotherapy. Both of these cases of adenocarcinoma of the cervix diagnosed in pregnancy showed estrogen receptor expression, a finding not typically seen in cervical adenocarcinoma.

2. Case 1

A 42 year old G3P1 woman was initially referred to colposcopy for Atypical Glandular Cells of Undetermined Significance (AGUS) on routine cervical cytology. Colposcopy revealed a suspicious lesion, which on biopsy was consistent with cervical Adenocarcinoma In Situ (AIS). The patient was subsequently found to be pregnant however an early first trimester ultrasound diagnosed a non-viable intrauterine pregnancy. The patient subsequently underwent a cone biopsy of the cervix, endocervical curettage, and dilatation and curettage of the endometrium. Final pathology from the cone biopsy revealed a well-differentiated invasive endocervical adenocarcinoma with depth of invasion of at least 3.0 mm and horizontal extent of at least 25.0 mm. The invasive carcinoma extended to the deep and peripheral excision margins. Products of conception were confirmed from the endometrial curettage. The patient was referred to Gynecologic Oncology and opted for definitive surgical management including radical hysterectomy, bilateral salpingectomy, and bilateral sentinel pelvic lymph node biopsy via laparotomy. Final pathology revealed a well-differentiated endocervical adenocarcinoma, usual type, with depth of invasion of 2 mm, horizontal extent 4 mm and involvement of the inner one third of the cervical stroma. There was no lymphovascular space invasion (LVSI). All margins and sentinel lymph node biopsies were negative for malignancy. Immunohistochemistry (IHC) staining for p16 and Estrogen Receptor (ER) were both positive (Fig. 1). The patient did not require adjuvant therapy. The patient remains disease-free 16 months following definitive surgical management.

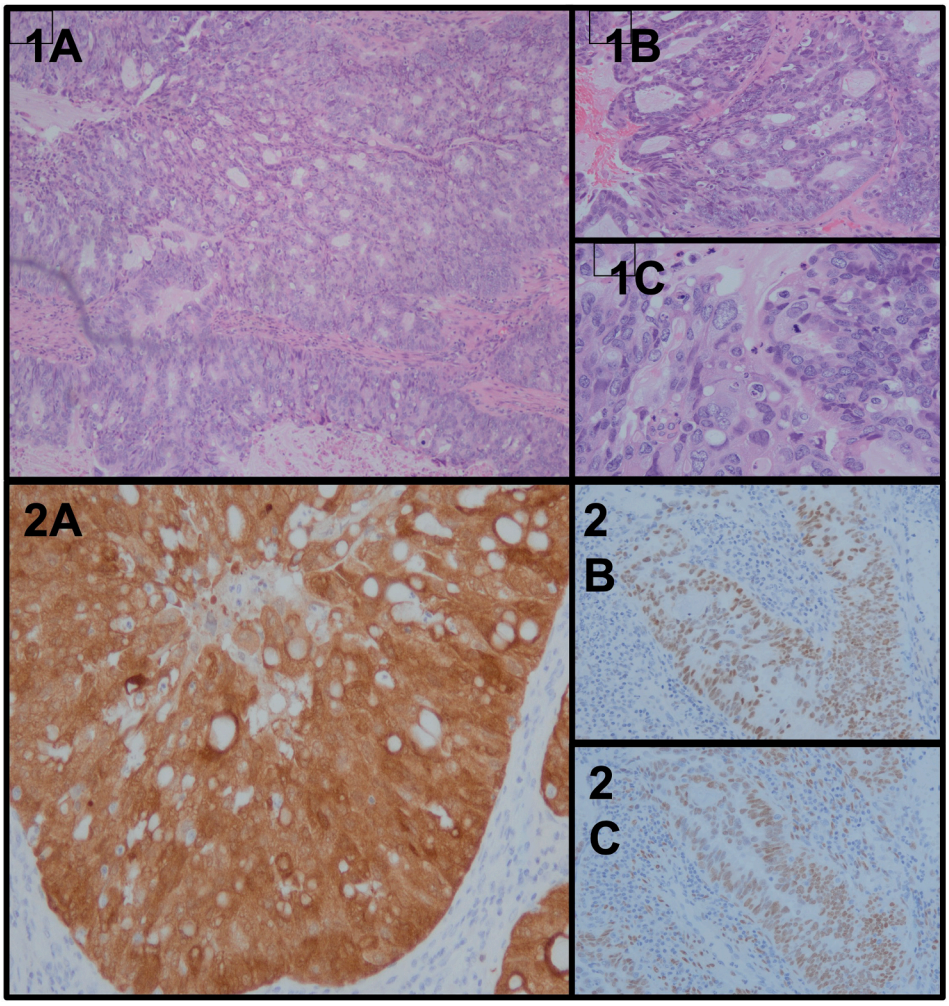

Fig. 1. Case 1 – H&E stain. (1A) Complex endocervical intraglandular growth (cribiform) X40, (1B) Confluent glandular growth ×100, (2C) Showing malignant endocervical cells with atypia and mitosis ×200. **Immunohistochemical staining.** (2A) P16 is overexpressed with nuclear and cytoplasmic staining ×100, (2B) Estrogen receptor staining the malignant cells nuclei ×100, (2C) Progesterone receptors highlighting the malignant cells nuclei ×100.

3. Case 2

A 36 year old G2P1 woman presented with antepartum hemorrhage at 29 weeks gestational age (GA) in an otherwise uncomplicated pregnancy. Initial ultrasound did not identify any abnormalities. Another episode of vaginal bleeding at 31 weeks GA prompted the identification of a large protruding cervical mass. Characterization with ultrasound and Magnetic Resonance Imaging (MRI) revealed a 52 × 47 × 50 mm pedunculated, exophytic mass favouring cervical polyp or fibroid originating from the inferior wall of the endocervix (Fig. 2).

The patient had undergone regular cervical screening as per national guidelines and screening to date had been unremarkable. The last cervical cytology was obtained early in the first trimester. The patient went on to undergo resection of the pedunculated mass at the time of elective repeat cesarean section and tubal ligation at 37 weeks and 6 days GA. The cervical mass was removed by placing two endoloops at the base of the mass, after which the mass was dissected off its base. Final pathology revealed an adenocarcinoma of the cervix measuring 8.5 × 8.0 × 2.0 cm with IHC staining positive for ER/Progesterone Receptor (PR), CK7, PAX8, and p16 consistent with mucinous differentiation (Fig. 3). This was further supported by a positive HPV-18 result via linear array HPV DNA genotype testing. There were findings highly suspicious for LVSI and invasion into the cervical stroma was seen.

The patient was referred to Gynecologic Oncology. Further imaging with Computed Tomography (CT) and Positron Emission Tomography (PET) scans did not reveal any evidence of local or distant metastatic disease and the Multidisciplinary Cancer Conference consensus was to proceed with definitive surgical management with radical hysterectomy, bilateral pelvic lymph node dissection and ovarian transposition. This was performed via a combined laparoscopic and laparotomy approach. The final pathology revealed a residual 12 mm moderately differentiated mucinous adenocarcinoma involving the cervical stroma with a depth of invasion of 2.2 mm and a horizontal extent of 10 mm. The tumor was arranged in fronds of cribiforming glands infiltrating into the cervical stroma with remnants of uninvolved cervical epithelium identified. Tumour cells were positive for ER/PR, p16, PAX8, CD7, and CD19 and negative for Vimentin, CEA, p53, CK 20, p63, HNF, and WT1. This result was consistent with a Not Otherwise Specified (NOS) mucinous subtype. The specimen was also HPV-18 positive on genotype testing. There was no LVSI identified in this specimen. All resection margins were negative, parametrium was negative, and all lymph nodes (LNs) were negative (0/27) for metastatic disease.

The pathology findings were discussed at the MCC conference. While not definitively fulfilling Sedlis criteria (Sedlis et al., 1999), since the originally excised primary tumour measured over 5 cm, the depth of invasion in the final hysterectomy specimen was likely underestimated. Consequently, the patient received external beam radiotherapy (EBRT) and completed 4500 cGy in 25 fractions to the pelvis using the Volumetric Modulated Arc Therapy (VMAT) technique. The patient is currently disease-free two years following adjuvant pelvic radiotherapy.

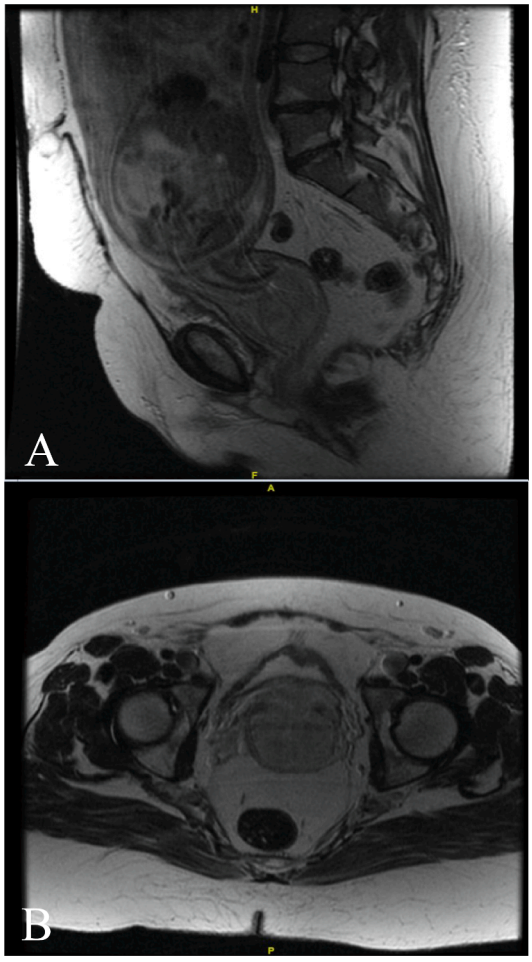

Fig. 2. Case 2 – MRI of Cervical Mass. (A) Sagittal T2-weighted image of mass in upper vagina measuring 52 × 47 × 50 mm in transverse, antero-posterior, cranio-caudal dimensions, respectively. (B) Axial T2-weighted image of mass in upper vagina.

4. Discussion

The optimal management of cervical malignancies during pregnancy remains unclear owing to its relative rarity. Once diagnosed, the treatment dilemma centres around balancing fetal viability (if periviable), fetal lung maturity, and morbidity associated with prematurity versus minimizing the risk of maternal disease progression. A retrospective study by Takushi et al. revealed that the majority of cervical malignancies during pregnancy are diagnosed in stage I (79%) (Takushi et al., 2002). Based on their retrospective data, treatment delays of up to 32 weeks were reasonable and did not result in tumor progression for women diagnosed with up to stage IB1 disease (FIGO 1995). However, these recommendations were made based predominantly on data from patients with SCC histology.

Adenocarcinoma of the cervix is a heterogenous group of tumours that can be divided into HPV-associated (HPVA) and non-HPV-associated (NHPVA) variants based on the 2017 IECC system (Stolnicu et al., 2019). HPVA cervical adenocarcinoma are less frequently associated with LVSI, lymph node metastases, and Silva C pattern on histology and typically are associated with better overall survival, disease-free survival, and progression-free survival and lower risk of recurrence (Stolnicu et al., 2019). HPVA may be further subdivided into usual types, which includes villoglandular and micropapillary architectural variants, and mucinous types, which include NOS, intestinal, signet ring, and invasive stratified mucin-producing carcinoma (Park, 2020).

In our two aforementioned cases, the immunohistochemistry revealed ER and p16 expression. While p16 expression is consistent with HPV-associated transformation as seen in the majority of cases of cervical carcinoma, the ER expression introduced a diagnostic dilemma. High-risk HPV-related endocervical adenocarcinomas are typically negative for ER/PR expression (Stewart et al., 2019). HPV testing was therefore performed, as proposed by Staebler et al. (2002) to differentiate endocervical and endometrial adenocarcinomas. Of note, endometrial mucinous adenocarcinomas can show aberrant prominent p16 expression (Stewart et al., 2019), emphasizing the importance of human papillomavirus DNA detection to aid in the distinction of endometrial and endocervical carcinomas. Positive vimentin and negative CEA can also be used to suggest a tumour originating from the endometrium.

In the context of pregnancy, it is conceivable that ER expression may lead to more rapid tumour growth. However, in our experience, these tumours favour a well-differentiated histology. In review of the

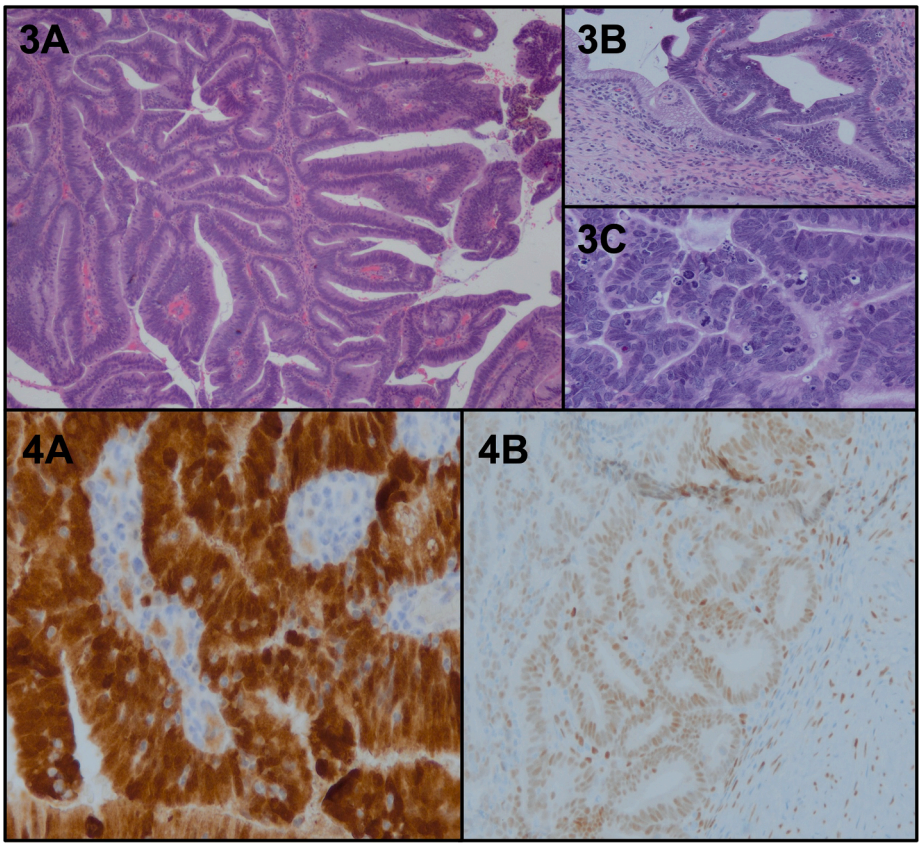

Fig. 3. Case 2 – H&E stain: (3A) Complex closely packed endocervical glands ×40. (3B) Transformation from normal to malignant endocervical cells, ×100. (3C) Malignant glands with cellular atypia mitosis, ×200. **Immunohistochemical staining**: (4A) P16 is strongly staining the nuclei and the cytoplasm, ×200. (4B) Estrogen receptor staining the nuclei, ×200.

literature, two other reports of mucinous adenocarcinoma of the cervix diagnosed during pregnancy favoured delayed treatment in favour of fetal maturation (Dolci et al., 1999, de Lima et al., 2013). In Dolci et al., the patient was found to have a cervical lesion at 28 weeks, which was not biospsied during preganncy, and she managed conservatively until delivery. Postpartum, colposcopy with biopsy was performed and pathology revealed mucinous papilliferous adenocarcinoma. The patient subsequently underwent conization followed by Type II radical hysterectomy and remained disease-free until publication of the case report. In Almeida de Lima et al., the patient was diagnosed at 23 weeks GA with biopsy of the cervical mass measuring approximately 4 cm showing invasive moderately differentiated mucinous adenocarcinoma of endocervical type at clinical stage 1B1. Owing to the extreme prematurity, the patient was treated with 2 cycles of neoadjuvant cisplatin and vincristine at 26 and 30 weeks GA, with partial response, followed by cesarean-radical hysterectomy and pelvic lymphadenectomy at 34 weeks GA. Pathologically, there were no involved pelvic lymph nodes and parametria were negative. The patient received 4 further cycles of chemotherapy. The patient remained disease-free 2 years after initial diagnosis. There are other reports of adenocarcinoma of the cervix diagnosed during pregnancy including villoglandular papillary adenocarcinoma subtypes that were managed conservatively with delivery at or near term (Lavie et al., 2007).

In Case 2, the cervical lesion was identified at 31 weeks GA, however the diagnosis of Stage IB2 mucinous cervical adenocarcinoma was not made until resection of the exophytic pedunculated mass at the time of elective repeat cesarean section at 37 weeks and 6 days GA. We hypothesize that this ER positive tumor rapidly increased in size (from 6 × 5 cm to 8.5 × 8 cm in 6 weeks) during pregnancy due to high levels of circulating estrogen in pregnancy. The patient was subsequently referred to Gynecologic Oncology and definitive radical hysterectomy was performed after a treatment delay of 17 weeks. The patient received adjuvant EBRT.

5. Conclusion

In summary, it is important to consider cervical primary in the work up of cervical adenocarcinoma in pregnancy despite potential ER positivity. Treatment should take into consideration gestational age, obstetrical complications, histological features, stage, and patient wishes with respect to the outcome of the pregnancy. A multidisciplinary team including Pathology, Gynecologic Oncology, Radiation Oncology, Medical Oncology, Radiology, and Maternal Fetal Medicine should be engaged in treatment planning and decision-making. Surveillance with MRI may be useful to confirm tumor size and depth of stromal invasion as well as to rule out parametrial or local invasion and lymph node involvement in patients who opt for delayed definitive therapy. As more cases of ER-positive adenocarcinoma of the cervix are discovered in the pregnant patient population, a greater understanding of the effect of pregnancy hormone on growth and safety of conservative management in favour of increasing fetal maturity will be achieved.

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 on request.

CRediT authorship contribution statement

James C.M. Wang: Conceptualization, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Laurence Bernard:** Conceptualization, Data curation, Formal analysis, Supervision, Writing – original draft, Writing – review & editing. **Odette**

Boutross-Tadross: Data curation, Formal analysis, Funding acquisition, Writing – review & editing. **Sarab Mohamed:** Data curation, Formal analysis, Writing – review & editing. **Sarah Alghamdi:** Data curation, Formal analysis, Writing – review & editing. **Amir Salehi:** Data curation, Formal analysis, Writing – review & editing. **Monalisa Sur:** Data curation, Formal analysis, Funding acquisition, Writing – review & editing. **Lorraine Elit:** Data curation, Writing – review & editing. **Lua R. Eiriksson:** Conceptualization, Supervision, Validation, Writing – review & editing.

Declaration of Competing 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.

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