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Case Series
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Cervical Cancer in Pregnancy: A Case Series

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Abstract

The management of cervical cancer in pregnancy is a major challenge due to the rarity of the condition limiting available evidence to guide recommendations. This case series aims to contribute to literature by documenting three cases of cervical cancer in pregnancy with delayed definitive treatment including a case of International Federation of Gynecology and Obstetrics (FIGO) stage 1B2 endocervical adenocarcinoma diagnosed at 18 weeks' gestation, a case of FIGO stage 1A1 squamous cell carcinoma of the cervix with lymphovascular invasion diagnosed at 20 weeks' gestation and a rare case of FIGO stage 1B2 villoglandular adenocarcinoma of the cervix diagnosed at 28 weeks' gestation. The short- to medium-term follow-up of these patients are promising.

Keywords: Cervical cancer; Pregnancy; Chemotherapy; Staging; Treatment

Introduction

Cervical cancer is the most commonly diagnosed gynecological malignancy in pregnancy with an estimated incidence of 0.8 to 1.5 cases per 10,000 births [1-3]. Most patients are diagnosed at an early stage of the disease [4] perhaps as a result of effective routine prenatal screening; however it is also possible that advanced stage disease may affect conception. Stratified for stage, the course of disease and prognosis of cervical cancer in pregnant women mirror that of their non-pregnant counterparts. Due to the rarity of the condition, management guidelines have relied on evidence from randomized trials in non-pregnant women and results from observational studies of pregnant women with individualized treatment based on the histological subtype, stage of cancer, and gestational age at diagnosis, the woman's preference for continuing the pregnancy and the inherent risks of modifying or delaying treatment in pregnancy.

With this in mind, this case series aims to contribute to literature and future research by documenting the management outcomes of three cases of cervical cancer in pregnancy of different histological subtypes, International Federation of Gynecology and Obstetrics (FIGO 2018) stages and gestational ages at diagnoses. Short- to medium-term outcomes for these patients have been excellent thus far.

Case Series

Case 1: A case of FIGO stage 1B2 endocervical adenocarcinoma diagnosed at 18 weeks' gestation

Patient A was a 33-year-old Gravida 2, Para 1 originally from East Timor, who was 16 weeks pregnant when she presented to the emergency department with her first episode of unprovoked vaginal bleeding. Speculum examination revealed an exophytic, friable, fungating mass arising from the posterior cervical lip measuring 2 cm × 2 cm in size. An urgent referral to the colposcopy clinic was made and the histopathology from a colposcopy-guided biopsy performed at 18 weeks' gestation showed a tumour with diffuse strong p16 staining, with morphology favoring poorly differentiated endocervical adenocarcinoma of the usual type.

Patient A had one previous uncomplicated term vaginal delivery eighteen months prior to presentation. She denied any history of intermenstrual or post-coital bleeding and had never had a Cervical Screening Test (CST). She was a never smoker.

This case was discussed at our Gynecological Oncology Multi-Disciplinary Team (MDT) meeting. A pelvic Magnetic Resonance Imaging (MRI) scan showed no evidence of a cervical lesion; no evidence of lymphadenopathy, parametrial or pelvic sidewall masses. The consensus recommendation was for Neoadjuvant Chemotherapy (NACT) prior to definitive local treatment

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with the aim for delivery of her baby *via* a caesarean section at 32 to 34 weeks gestation after steroid administration for fetal lung maturity. At 20 weeks gestation she was reviewed by her medical and gynecological oncologists in outpatient clinic and this recommendation was discussed. She was keen to proceed with the pregnancy.

Patient A subsequently underwent an Examination under Anesthesia (EUA), cystoscopy and rigid sigmoidoscopy at 21 weeks gestation. An exophytic tumour of the posterior lip measuring 3 cm with no parametrial extension was noted; there was no evidence of bladder, anal or rectosigmoid involvement. She was clinically staged as stage 1B1 (FIGO 2018).

The pregnancy was complicated by the development of early Fetal Growth Restriction (FGR) with a fetal abdominal circumference noted to be less than the 7th centile on ultrasound scan at 20 weeks, and by gestational diabetes which was controlled with metformin 500 mg once daily. The patient was referred to the hospital's Maternal-Fetal Medicine (MFM) unit for ongoing fetal surveillance. An ultrasound scan performed at 24 weeks gestation revealed a fetus with an Estimated Fetal Weight (EFW) on the 44th centile with normal Doppler indices and amniotic fluid volume measurements. At 28 weeks gestation the EFW was 1083 g (on the 18th centile) with normal Doppler indices and amniotic fluid volume.

In agreeance with the recommendations from the MDT, the patient commenced her first cycle of NACT with carboplatin and paclitaxel at 23 weeks gestation. No clinical response was noted after her second cycle of chemotherapy at 26 weeks gestation. She completed her third cycle by 29 weeks' gestation and proceeded to undergo an uncomplicated transverse lower uterine segment caesarean delivery of a 2018 g neonate at 33+5 weeks gestation. Follow-up colposcopy six weeks post-partum unfortunately showed persistent disease. A staging 18F-Fluorodeoxyglucose (FDG)-PET/CT scans revealed localized disease only.

After extensive counseling patient A decided on surgical management with an open radical (type II) hysterectomy, bilateral salpingo-oophorectomy, pelvic lymph node dissection and omental biopsy at eight weeks post-partum. Intra-operative findings showed a 3 cm to 4 cm cervical mass with no gross vaginal or parametrial involvement. There was no evidence of gross pelvic or para-aortic lymphadenopathy. Histopathology results revealed a 25 mm well-differentiated adenocarcinoma of the cervix with positive Lymphovascular Invasion (LVSI), and one positive left parametrial lymph node (1/10). The surgical margins were clear and the pelvic lymph nodes were negative.

After further MDT review, she was restaged FIGO stage 1B2 adenocarcinoma of the cervix and it was recommended that she undergo adjuvant pelvic chemo-radiotherapy (weekly cisplatin chemotherapy and adjuvant pelvic radiotherapy (45 Gy/25 fractions)) which was completed three months post-operatively.

The patient has remained clinically free of any evidence of loco-regional recurrence at her three- and six-months' follow-up. She uses estrogen hormone replacement patches with good effect and has ongoing follow-up organized with both her radiation and gynecological oncology treating teams at three-month intervals.

Case 2: A case of FIGO stage 1A1 cervical Squamous Cell Carcinoma (SCC) diagnosed at 20 weeks gestation

Patient B was a 40-year-old Gravida 12, Para 8 who was 20 weeks' pregnant when she was reviewed at our colposcopy clinic. She had been referred with an asymptomatic high risk cervical screening test result showing HPV 16 positivity, and cytology suggestive of a High-Grade Squamous Intra-Epithelial Lesion (HSIL). The patient had had an uneventful pregnancy so far. The patient's obstetric and gynecological history included eight vaginal deliveries at term. She was due for a CST with the last test being performed "a few years ago" that was unremarkable. She denied a history of post-coital and inter-menstrual bleeding. The patient had the same sexual partner for twenty years, with no history of sexually transmitted diseases or pelvic inflammatory disease. Her family history was low risk for a gynecological malignancy. She was a smoker with a 5 pack-year smoking history. On colposcopic examination, a type one transformation zone was noted with dense acetowhite staining in all four quadrants. Marked punctations and mosaicism were noted on the anterior cervical lip where a biopsy was performed. The overall impression was that of a high-grade lesion. The histopathology results from the biopsy showed a focal early invasive SCC with a Depth of Invasion (DOI) at 0.8 mm, CIN 3 and HPV present. A pelvic MRI showed no evidence of cervical or pelvic masses and no evidence of lymphadenopathy.

The case was discussed at our Gynecological Oncology MDT meeting. The consensus was to offer either a cone biopsy or conservative management with frequent colposcopies ± biopsies and a planned delivery at 32 to 34 weeks gestation to optimize fetal maturity.

The patient subsequently had her first review with the Gynecological Oncology team at 22 weeks' gestation. The provisional diagnosis of early stage 1A1 cervical SCC was discussed. The standard of care being a cone biopsy for both diagnostic and potentially therapeutic purposes was also discussed, acknowledging the risk of pregnancy complications including miscarriage and preterm labor (and its inherent risks of neonatal morbidity and mortality). The alternative management of repeat colposcopies every two weeks, aiming for a delivery at 32 to 34 weeks gestation then performing a cone biopsy and review for further management was also discussed. At that appointment, the option for termination of pregnancy (as the fetus was at a pre-viable gestation) followed by a cone biopsy was also discussed. A colposcopy and biopsy performed that day confirmed the findings on referral colposcopy and histopathology.

At her subsequent appointment at 25 weeks' gestation, after further counseling and consideration, the patient opted for conservative management, understanding the risk of missing a higher stage malignancy with this management. The patient underwent a colposcopy that day which remained stable from her last review.

A biopsy was performed at the final colposcopy review at 27 weeks gestation, due to the presence of a lesion suspicious for invasive disease. The histopathology showed invasive SCC (DOI 0.4 mm). A decision was made not for a further colposcopy but to await delivery which occurred at 32+5 weeks' gestation *via* an uncomplicated transverse lower uterine segment caesarean delivery of a live born, weighing 1815 g with good Apgar scores.

An examination under anesthesia, colposcopy, and cone biopsy and endocervical curettage were performed four weeks post-partum. The clinical findings included high grade changes in four quadrants with no evidence of gross invasive disease. The histopathology from the cone biopsy showed a well-differentiated squamous cell carcinoma,

with DOI 1.3 mm, and 6 mm maximal in the horizontal dimension. One focus of LVSI was present and there was a background area of HSIL. The resection margins were free of SCC and HSIL (closest 6 mm stromal margin). The endocervical curettings showed no evidence of malignancy. The patient underwent a staging FDG-PET/CT scan two weeks post-operatively which showed moderate focal activity in the region of the uterine cervix indicating the primary tumor however a note was made that it could also represent inflammatory changes in the setting of the recent biopsy. No evidence of metabolically active regional nodal or distant metastasis was seen.

The case was discussed in the Gynecological Oncology MDT where the radicality of the hysterectomy and the role of lymph node dissection in the setting of early-stage cervical cancer with positive LVSI and free cone margins where all discussed. A second opinion was sought from another centre due to the contentious nature of the condition. The consensus was for a simple hysterectomy with pelvic lymph node dissection/assessment. There was no consensus regarding the surgical approach and it was left to the surgeon to discuss open *vs.* minimally invasive techniques with the patient.

Patient B subsequently underwent an uncomplicated robotic-assisted simple hysterectomy, bilateral salpingectomies (with ovarian preservation due to her low-risk family history) and sentinel lymph node biopsies. Intra-operative findings included a normal uterus, fallopian tubes and ovaries; bilateral sentinel lymph nodes were identified (left and right infra-mesenteric para-aortic lymph nodes) with a prominent right external iliac node with late indocyanine green uptake -all of these nodes were excised and sent for histopathology. A cystoscopy was performed which was unremarkable. The patient was re-admitted six days post-operatively with abdominal pain, nausea and vomiting. A CT scan showed a small pelvic collection which subsequently drained spontaneously per vagina. The patient received 24 h of intra-venous antibiotics during her admission and was discharged home the following day with a course of oral antibiotics.

Histopathology from the hysterectomy showed no residual squamous cell carcinoma or HSIL, with no evidence of malignancy in the excised lymph nodes. No malignant cells were seen in the peritoneal washings. The results were discussed at the MDT and the consensus was that no further treatment was required.

Patient B has remained well at her follow-up appointments at two weeks, four weeks and six months with no evidence of systemic lymphadenopathy. Her next follow-up is scheduled in six months' time.

Case 3: A case of FIGO stage 1B2 Villoglandular Adenocarcinoma (VGA) of the cervix diagnosed at 28 weeks' gestation

Patient C was a 31-year-old Gravida 4, Para 2 who was 28+5 weeks pregnant with spontaneously conceived Dichorionic Diamniotic (DCDA) twins when she was transferred to our tertiary centre with biopsy-proven well-differentiated VGA with diffuse strong immunohistochemical staining for p16, favoring an endocervical origin. This was diagnosed at 28+2 weeks' gestation when she presented to her local hospital with a history of unprovoked vaginal bleeding associated with mild abdominal cramps and a "lump coming out from vagina". On examination a 6 cm × 7 cm exophytic, friable mass was seen protruding from her vagina rendering a speculum examination impossible. Tissue was sent from this mass for histopathological examination. In view of the vaginal bleeding and cramps, the patient was administered steroids for fetal lung maturation in the setting of threatened preterm labor. The pregnancy was complicated by gestational diabetes which was well-controlled with dietary modification, and by mild hyperthyroidism. She had two previous uncomplicated term vaginal deliveries. Her last Papanicolaou smear had been performed less than two years ago and was negative. Her other medical history included asthma and cholecystectomy. She was not prescribed any regular medications. She had one stable sexual partner and she smoked 8 cigarettes a day in the pregnancy.

Prior to her admission at 28+2 weeks gestation, she reported unprovoked vaginal spotting since 5 weeks' gestation. This was initially attributed to a 28 mm × 4 mm × 11 mm subchorionic hematoma which eventually resolved on serial ultrasound scans. A speculum examination was eventually performed at 18 weeks' gestation when the patient presented with heavier per vaginal bleeding. A "cauliflower-like" lump (not measured) was noted over the cervix. The patient declined a biopsy at the time so a small amount of tissue on blood-soaked gauze was sent for histopathology examination which returned inconclusive. The patient declined a biopsy again, despite counseling, at 21 weeks' gestation. An obstetric ultrasound scan performed at 24 weeks gestation showed concordant fetal growth and note was made of a heterogeneous lesion in the cervix, with calcification, measuring 45 mm × 31 mm × 28 mm. A plan was made to review her again at 32 weeks gestation with serial ultrasound scans in the interim. The patient, however, presented to the same hospital at 28+2 weeks gestation and subsequently transferred to our service with a biopsy-proven diagnosis at 28+5 weeks gestation.

On admission, the patient was reviewed by the Gynecological Oncology team. She underwent a pelvic MRI which showed an exophytic cervical mass involving the right vaginal fornix and parametrial involvement was not excluded. She proceeded to undergo an examination under anesthesia and cystoscopy the following day, at 29 weeks gestation. The clinical findings were that of a fungating tumour measuring 8 cm × 6 cm × 5 cm arising from the anterior cervical lip and 2 cm × 2 cm × 2 cm arising from the posterior lip. There was no obvious vaginal spread. The right uterosacral ligament felt shortened; the left parametria was not involved. A suspicious lesion near one of the ureteric orifices was biopsied. Biopsies of the cervical tumor confirmed adenocarcinoma with a villoglandular morphology; the biopsy from the lesion near the ureteric orifice returned with Brunn's glands and cystitis glandularis.

Due to the rarity of the patient's subtype of cervical cancer, Gynecological Oncology colleagues were consulted at two different centers for further opinion. The recommendations from these discussions were offered to the patient who attended the Gynecological Oncology MDT meeting two days post-operatively at 29+2 weeks gestation. Also present were the treating Gynecological Oncology team, a Medical Oncologist, a Radiation Oncologist, a "High-risk Obstetrics" midwife and a clinical psychologist. The options for NACT followed by a planned classical caesarean section at 33 to 34 weeks gestation to allow fetal maturity, or a planned classical caesarean section delivery without delay followed by post-partum chemoradiotherapy were discussed. The patient opted for the former. Serial ultrasound scans for fetal growth and well-being were also scheduled with our MFM team and were unremarkable apart from the vascular cervical mass.

Patient C later received one cycle of carboplatin and paclitaxel at

30 weeks gestation followed by an uncomplicated classical caesarean section delivery of her twins at 34 weeks gestation with a rescue dose of steroids administered prior. An intra-operative assessment by a Gynecological Oncologist was performed at the end of the caesarean section to assess the tumour response to chemotherapy – a good response was documented with the anterior cervical mass measuring 6 cm at its largest diameter. No parametrial involvement was noted.

The patient proceeded with three cycles of chemotherapy, commencing one-week post-partum, with excellent tumour response. On review after her third cycle of chemotherapy, it was noted that there was no exophytic tumor remaining with the mass measuring less than 4 cm and clinically confined to the cervix. An FDG-PET/CT scan performed six weeks post-partum showed active residual disease confined to the cervix. After discussion at the MDT, the recommendation was for open radical hysterectomy with bilateral salpingectomy, bilateral ovarian transposition, bilateral pelvic lymph node dissection and cystoscopy, which the patient underwent eight weeks post-partum.

Intra-operative findings were that of a normal uterus, bilateral fallopian tubes and ovaries and the enlarged cervix with malignancy. An anterior abdominal peritoneal adhesion was resected for histopathology. An extensive left ovarian vein thrombus extending from its origin along the left infundibulopelvic ligament up to the renal vein with associated erythema and swelling was also seen. A vascular surgical opinion was sought intra-operatively - the thrombus was thought to be chronic. The patient was thus treated with intravenous heparin 2500 IU. A urological opinion was also sought intra-operatively due to concerns regarding thermal spread from a diathermy instrument which was activated close to the right ureter. Cystoscopy performed confirmed bladder integrity; bilateral ureteric stents were passed easily and palpated abdominally. Due to concerns regarding thermal injury to the right ureter, only the left ureteric stent was removed at the end of the procedure.

The histopathology confirmed VGA of the cervix. Clear surgical margins were achieved and lymph nodes sampled were negative (0/13). The abdominal wall nodule was unremarkable. The consensus decision after discussion at the MDT meeting was not to offer adjuvant radiotherapy given the low risk of recurrence.

The patient experienced an uneventful post-operative recovery having passed her trial of void on day two. She was discharged with 6 weeks of prophylactic low molecular weight heparin and a plan for a repeat CT scan. Her right ureteric stent was removed 4 weeks post-operatively without complication.

Patient C was followed up three-monthly for the subsequent eighteen months, and six-monthly for the following two years. To date, there has been no evidence of locoregional recurrence, with repeat negative vault co-tests for HPV and cytology. The patient's twins are also reportedly healthy. She will be reviewed next in six months' time and understands the requirement for lifelong annual vault co-tests in view of her adenocarcinoma histopathological diagnosis.

Discussion

The management of cervical cancer in pregnancy presents a major challenge. Before 20 weeks gestation, surgical management or radiotherapy with the fetus *in situ* has been shown to be safe and effective for early-stage cervical cancer but it results in termination of pregnancy. NACT is a potential treatment option as it results in significant tumour regression or stabilization and may be of value in pregnancy to ensure fetal viability and maturity. The fetal effects of NACT depend on the gestational age, agent(s) used and dosage [5].

NACT is generally avoided until completion of organogenesis at 13 weeks' gestation as approximately 10 % to 20% of children exposed to cytotoxic agents in the first trimester have major congenital malformations (*vs.* 3% in the general population) [5-7]. Although the use of NACT is considered to be relatively safe in the second and third trimesters, the long-term neurologic effects from exposure to a neurotoxic drug before 28 weeks' gestation are not known. Furthermore, there is evidence that the use of NACT in pregnancy may be associated with intrauterine growth restriction and low birth weight [8,9]. Reassuringly, despite the lack of long-term follow-up data, no abnormalities have been found thus far in children born to mothers treated with NACT in pregnancy [10-17]. Patients motivated to continue with the pregnancy, as in the cases of Patients A and C, therefore require extensive counseling to assist them in making an informed decision regarding NACT. The long-term follow-up of any clinical effects of NACT on the children of patients A and C will undoubtedly add value to future research.

There is continuing interest in the role of Sentinel Lymph Node (SLN) biopsy in selected patients with early-stage cervical cancer, as in the case of patient B. Perhaps its greatest advantage is the reduction of morbidity associated with comprehensive surgical dissection of pelvic lymph nodes [18]. The sensitivity of SLN biopsy for identifying nodal metastases was 81% in one meta-analysis which increased to 99% (95% CI 98% to 100%) with a negative predictive value of 97% to 100% when the analysis included only patients with tumors <4 cm in size, negative pre-operative imaging and in whom bilateral SLNs were detected intra-operatively with ultra-staging performed on sentinel node specimens [19]. SLN biopsy also appears to perform better than imaging studies [20], further adding to its appeal. Further evidence from prospective clinical trials would be beneficial in informing the clinical application of SLN biopsy in selected cervical cancer patients.

The case of patient C is a rare case of VGA of the cervix- a subtype of cervical adenocarcinoma that accounts for 3.7% to 4.8% of all cervical adenocarcinomas [21,22]. As of 2014, approximately 150 cases were reported in international literature [23]. The etiology of VGA remains unknown however some studies have suggested a role for HPV infection in the pathogenesis [24,25]. Limited data in literature suggest that VGA of the cervix is often indolent, and surgical management often provides a favorable outlook [26,27]. VGA has been associated with superficial invasion, rare lymphovascular invasion and infrequent lymph node metastasis, prompting some surgeons to conduct fewer radical surgeries such as conization [28-32]. Our Patient C underwent radical surgery with ovarian preservation due to evidence of active residual disease on an FDG-PET/CT scan following three cycles of NACT. She has enjoyed favorable medium-term outcomes thus far.

Apart from the interesting and rare diagnosis of villoglandular adenocarcinoma of the cervix in pregnancy, the case of patient C also highlights the pitfalls of delayed diagnosis as her vaginal bleeding was initially attributed to a sub-chorionic hematoma. In two series, 50% of pregnant patients with stage 1B disease were asymptomatic at the time of their diagnosis and had their disease detected by routine cervical screening [3,33]. Patients with symptomatic stage 1B disease commonly presented with abnormal per vaginal bleeding or

discharge; patients with advanced disease also presented with pelvic pain, chronic anemia and shortness of breath- symptoms similar to those associated with a normal pregnancy. Judicious history taking and examination cannot be understated.

Finally, this case series reinforces the importance of routine prenatal cervical cancer screening. Screening has contributed to a decline in mortality rate from cervical cancer in the past few decades however it remains a major cause of death in women worldwide.

Conclusion

Despite being the most common gynecological malignancy diagnosed in pregnancy, cervical cancer remains relatively rare and individualized management plans should be formulated in the setting of a multidisciplinary team. Contributions from obstetrician, gynecological oncologist, and medical and radiation oncologist as well as an MFM unit in a collaborative manner and incorporation of the patient's personal preferences are key to optimizing the outcomes for the woman and her fetus. We have observed excellent short to medium term outcomes with our patients and this may aid in the counseling of future patients regarding treatment options.

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