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Small Cell Cervical Carcinoma in Pregnancy: Therapeutic Options for an Aggressive Cancer Diagnosis

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Abstract

Neuroendocrine small cell cervical carcinoma is an aggressive cancer which accounts for approximately 1 to 3% of all cervical neoplasms. Therapy must be altered in pregnancy to optimize maternal–fetal outcomes. A 39-year-old woman presented for a routine prenatal visit and was noted to have a grossly abnormal cervix. Cervical biopsies confirmed small cell carcinoma. At 19 weeks' gestation, chemotherapy was initiated. The patient delivered at 34 weeks' gestation to initiate radiation therapy. Six months later, she was diagnosed with metastatic disease and died from cancer complications. In pregnancy, treatment modalities for small cell cervical carcinoma are based on the patient's gestational age at diagnosis. While aggressive early treatment is preferred, platinum-based chemotherapy can be initiated in the second trimester and radiation therapy delayed until delivery. Small cell cervical carcinoma complicating pregnancy requires aggressive treatment. Chemotherapy in the second trimester with planned delayed radiation therapy, may optimize fetal outcomes.

Keywords

- small cell carcinoma
- cervical cancer in pregnancy
- small cell cervical carcinoma in pregnancy
- management
- small cell cervical cancer
- therapy

Neuroendocrine small cell cervical carcinoma is a rare and aggressive cancer that carries an exceptionally poor prognosis. Neuroendocrine tumors are a form of cancer that arise from endocrine glands and nerve cells. Tumors of this nature are considered a systemic disease and can produce hormones. Cases of neuroendocrine cancer arising from the cervix are extremely rare and account for approximately 1 to 3% of all cervical neoplasms.[1–3] As such, there are limited data on the incidence of this disease in pregnant women. Treatment in nonpregnant patients has traditionally mirrored small cell cancer of the lung, which is composed of radiation with adjuvant chemotherapy. However, in patients diagnosed in pregnancy, caution must be taken to ensure that pregnancy is maintained and risk to fetal development is minimized.[4–6] Our case highlights the treatment course of a patient who was incidentally found to have small cell cervical carcinoma during a routine prenatal visit.

Case

A 39-year-old G2P1001 presented for a routine prenatal visit at 13 weeks' gestation and was noted to have a grossly abnormal, lobular cervix. A Pap smear performed at that time revealed atypical glandular cells and was positive for human papillomavirus (HPV) 16. A subsequent magnetic resonance imaging (MRI) demonstrated a mass arising from the ectocervix measuring 4.0 cm × 3.0 cm × 3.3 cm. No lymphadenopathy or evidence of metastatic disease was

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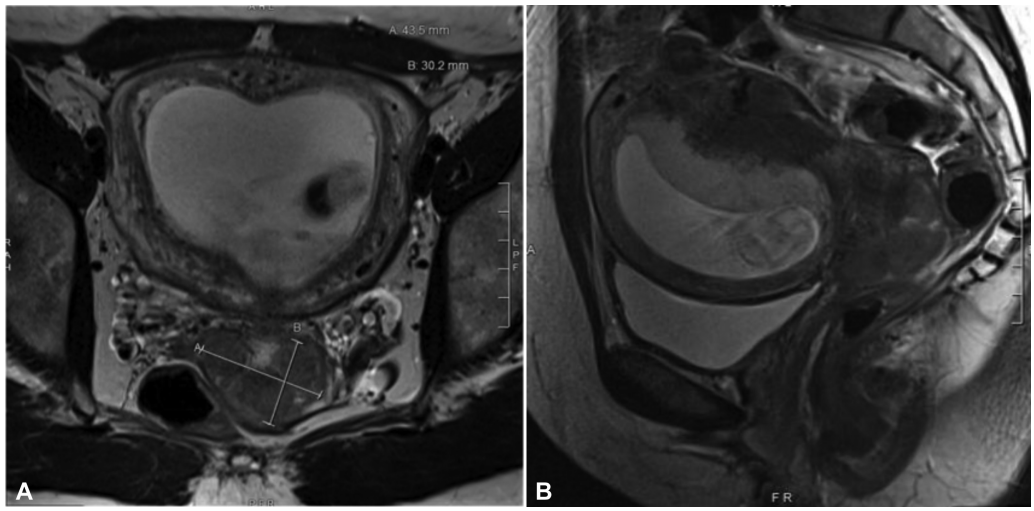

Fig. 1 Magnetic resonance imaging of 4.0 cm × 3.0 cm × 3.3 cm mass arising from the ectocervix. (**A**) Axial view. (**B**) Sagittal view.

noted (►**Fig. 1**). At 15 weeks' gestation, the patient underwent an examination under anesthesia. Cervical biopsies obtained at that time confirmed neuroendocrine small cell cervical carcinoma FIGO stage IB3. Immunoperoxidase stains for cytokeratin (CK) cocktail, cluster of differentiation (CD) 56, chromogranin, synapsin (Syn), and CDX2 were positive (►**Fig. 2**). Stains for CK5/6, thyroid transcription factor-1, and P40 were negative.

Given the reported poor prognosis for this cancer and need for urgent initiation of treatment, the patient was offered termination of pregnancy which she declined. Neoadjuvant chemotherapy was delayed until 19 weeks' gestation to decrease risks to developing fetus. She received five cycles of cisplatin 80 mg/m^2 and etoposide 100 mg/m^2. A decision was made to proceed with a preterm delivery at 34 weeks to expedite the initiation of radiation therapy. She received a standard 48-hour course of betamethasone for fetal lung maturity prior to delivery. She subsequently delivered at 34$^{2/7}$ weeks via repeat low transverse cesarean section. Neonatal Apgar scores were 8 and 9. The male neonate weighed 4 lb 14 oz and was admitted to our intermediate care nursery. The neonate was discharged home on day of life 10 with no neonatal complications. The patient's immediate postpartum course was also uncomplicated from an obstetric standpoint, and she was discharged home on postoperative day 3 after a routine postoperative course.

Four weeks following delivery, she began pelvic external beam radiation therapy. Midway through treatment, she was diagnosed with idiopathic thrombocytopenia with a platelet nadir of 13,000/µL. Radiation treatment was held until platelet levels rose to 60,000/µL after dexamethasone therapy. She resumed external beam radiation 8 weeks after radiation therapy was initially stopped. She received a total of 50.4 Gy in 28 fractions with a cumulative pelvic dose of 55.8 Gy. During this time, she was unable to receive concurrent chemotherapy due to persistent thrombocytopenia. A follow-up MRI revealed a residual tumor measuring 3.5 cm × 2.0 cm × 3.4 cm without parametrial extension.

A positron emission tomography scan performed 6 months later revealed interval development of widely metastatic disease in her axial and appendicular skeleton and innumerable hepatic metastases. A computed tomography–guided liver biopsy confirmed malignant metastatic small cell cervical carcinoma. The patient subsequently developed symptoms of drooling and slurred speech. A brain

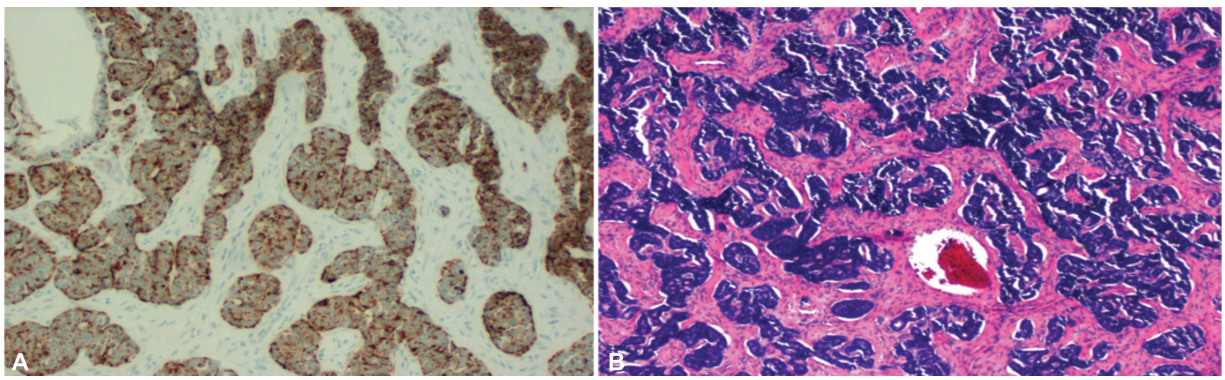

Fig. 2 (**A**) Hematoxylin and eosin–stained section revealing small cell cervical carcinoma with hyperchromatic nuclei and scant cytoplasm. (**B**) Positive CD56 immunoperoxidase stain. CD56 is a neuroendocrine marker classically found in small cell carcinoma of the lung. CD, cluster of differentiation.

MRI confirmed metastases involving cranial nerve XII. The patient elected to forgo further curative treatments and enrolled in hospice care. She succumbed to her disease 2 months later, 22 months after her initial diagnosis.

Discussion

Although the incidence of small cell cervical carcinoma is exceedingly rare, its inherent morbidity and mortality is associated with a universally poor prognosis, with estimated 5-year survival reported as less than 40%.[2,7,8] In fact, three separate studies observed a median survival for women with endocrine tumors of the cervix as a mere 22, 23, and 28 months versus 10 years for women with cervical squamous cell carcinoma.[3,9,10] This poor prognosis can be attributed to the typical rapid growth for this cancer and the capability for early metastatic progression with lymph node involvement. Gardner et al reported that 50% of patients had lymph node involvement at the time of diagnosis. In light of this, clinicians should consider comprehensive evaluation of the bones, supraclavicular lymph nodes, lung, liver, brain, and pancreas at the time of diagnosis.[2]

Patients with small cell cervical carcinoma commonly present with irregular vaginal bleeding, a palpable cervical mass, discharge, or severe lower abdominal pain. Due to the endocrine nature of the cancer, patients may less commonly present with paraneoplastic symptoms due to ectopic hormone production including Cushing's syndrome, syndrome of inappropriate antidiuretic hormone, or myasthenia gravis.[2] Diagnosis of small cell cervical carcinoma is performed via biopsy and immunohistochemical staining. The most common staining markers include neuron-specific enolase, Syn, CD56, and chromogranin A,[11] all of which were positive on our patient's biopsy.

Although there is a clear connection between the HPV and squamous cell carcinoma of the cervix, the association between small cell cervical carcinoma and HPV is controversial. Although our patient tested positive for HPV 16, in our review, Masumoto et al reported in a limited sample size of 10 patients diagnosed with both small cell cervical carcinoma and HPV that 9 of 10 were positive for the HPV 18 phenotype which is known to carry the Rb inactivating protein, E7.[12] However, further studies are necessary to elucidate any strong association.

Small cell cervical carcinoma has typically been treated similarly to small cell lung cancer with multiple rounds of chemoradiation with etoposide/cisplatin. Radical surgery can be considered in early-stage small cell cervical carcinoma (< 4 cm) in conjunction with adjuvant chemotherapy.[2,13–15] Radiation therapy can be considered in patients who are not candidates for surgery. Wang et al and Balderston et al reported complete remission with a combination of chemotherapy and radiation therapy in lieu of radical surgery, with Balderston et al utilizing a regimen of cisplatin/etoposide alternated with vincristine/dactinomycin/cyclophosphamide.[16,17]

Given the paucity of data on small cell cervical carcinoma in pregnancy, no standard treatments have been identified. The approach to treatment in pregnant patients must be individualized and should consider maternal desires to continue the pregnancy. Patients may elect to postpone treatment with chemotherapeutic agents until gestational advancement into the second or third trimester to avoid possible interference with organogenesis in the first trimester.[18] We recommend against delaying treatment until after delivery given the aggressive nature of small cell cervical carcinoma.

Survival rates of patients with pregnancy complicated by cervical cancer have been significantly lower than in nonpregnant patients with rates of 70 to 78% versus 87 to 92% after 5 years. This could be attributed to the pregnancy state accelerating the progression of cervical carcinoma due to immunological suppression in tandem with elevated estrogen levels and increased vascularity. As such, definitive therapy should be offered regardless of gestational age and expectant management should be discouraged.[6,17] In contrast to squamous cell cervical carcinoma which may allow for modest treatment delay due to pregnancy, immediate initiation of systemic treatment is recommended to improve maternal survival outcomes with the diagnosis of small cell cervical carcinoma.[5,16,19] In our case, chemotherapy was initiated in the second trimester to slow disease progression and preterm cesarean delivery was performed to allow earlier radiation therapy, affording our patient the best chance of prolongation of life.

This case highlights the importance of a multidisciplinary approach combining a maternal–fetal medicine specialist, a gynecological oncologist, a radiation oncologist, and the patient to weigh the risks and benefits of proceeding with chemotherapy prior to delivery and preterm delivery, with the potential benefit of expediting appropriate treatment of the mother to maximize chances for a favorable clinical outcome.

Conflict of Interest

None declared.

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