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CASE REPORT

Neuroendocrine Small Cell Uterine Cervix Cancer in Pregnancy: Long-Term Survival Following Combined Therapy

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A 22-year-old woman carrying twin gestations at 30 weeks presented with preterm labor and a prolapsing cervical mass. Following Cesarean section birth, she was treated with multiagent chemotherapy followed by pelvic radiotherapy for a Stage IIA small cell cancer of the uterine cervix. She is without evidence of disease 5.5 years after diagnosis and is the first reported long-term survivor of a small cell cervical carcinoma diagnosed during pregnancy.

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INTRODUCTION

Endocrine tumors account for only 1–2% of all uterine cervix cancers. A variety of descriptive terms have been used to account for the broad morphologic spectrum encountered, including neuroendocrine tumor, small cell carcinoma, oat cell carcinoma, carcinoid tumor, argyrophil cell carcinoma, and apudoma. In an effort to facilitate comparisons of the clinicopathologic characteristics and biologic behavior of these rare tumors, a workshop was sponsored by the College of American Pathologists and the National Cancer Institute to construct a uniform terminology system for the endocrine tumors of the uterine cervix [1]. The classification scheme developed is similar to that of the neuroendocrine tumors of the lung and includes the classical carcinoid tumor, the atypical carcinoid, the large cell neuroendocrine carcinoma, and the small (oat) cell carcinoma.

The small cell carcinomas are histologically indistinguishable from oat cell pulmonary cancer and portend a grave prognosis. More than half of patients with apparent early-stage disease have nodal involvement and most patients treated by radical surgery and radiotherapy succumb to widespread metastases [2]. Because of its poor prognosis and propensity for hematogenous spread, systemic chemotherapy is a mainstay of treatment of small cell carcinoma of the cervix, with many patients experiencing prolonged disease-free survival. We re-

port the first known survivor of a small cell cervical carcinoma diagnosed during pregnancy.

CASE HISTORY

In July 1992, a 22-year-old Caucasian woman, gravida 5, para 3, presented with preterm labor and a prolapsing cervical mass. She was carrying a twin gestation at 30 2/7 weeks. Her most recent Papanicolaou test had been performed 6 months previously at an outside facility and reportedly was within normal limits. A pelvic examination revealed an 8-cm, pedunculated, tan, friable mass arising from the anterior cervix, assumed to be a myoma. She was admitted and underwent intravenous tocolysis with magnesium sulfate. A course of intramuscular corticosteroids was administered. Ultrasonography demonstrated concordant twins with no anomalies, both in vertex presentation. The patient was kept at bedrest and the cervical mass was reduced. Several pessaries were fitted, but the mass continued to prolapse.

On the ninth hospital day, the patient was taken to the operating room for an examination under anesthesia which revealed an 8-cm friable, necrotic cervical mass extending into the upper vagina wall (Fig. 1). An acute hemorrhage prompted an emergency Cesarean section with delivery of viable twin female infants with birth weights of 1,625 and 1,800 g. The lower uterine segment was palpably normal and there was no gross disease in the abdomen or pelvis. A portion of the cervical mass was sent for pathologic analysis. Hemostatic sutures and a vaginal pack were placed to control bleeding.

The specimen was composed entirely of malignant cells without cystic spaces, papillary structures, or normal cervical mucosa. Small round cells with hyperchromatic nuclei and scant cytoplasm, characteristic of a small cell carcinoma of the uterine cervix, were observed (Fig. 2). Neurosecretory granules were present on electron microscopy. Immunohistochemistry

FIG. 1. Photograph of the cervical mass prior to excisional biopsy.

studies demonstrated tumor cells which stained positively with antibodies to cytokeratin and focally with antibodies to chromogranin. The tumor cells failed to stain with antibodies to synaptophysin. The placenta was without evidence of metastatic disease. Pelvic washings retrieved at the time of Cesarean section did not contain malignant cells.

Examination 3 weeks postpartum revealed an 8×10 cm friable fleshy cervical mass extending to the left vaginal fornix. There was no parametrial thickening or nodularity. A metastatic workup included a normal chest roentgenogram, bone scan, and cranial computed tomography. Abdominal and pelvic computed tomography showed no retroperitoneal or liver involvement.

From August to December 1992, the patient received three courses of cisplatin (80 mg/m^2) and etoposide (400 mg/m^2) alternating with two courses of VAC: vincristine ($1.2 \text{ mg/m}^2/\text{wk} \times 3$ weeks), dactinomycin ($300 \mu\text{g/m}^2/\text{day} \times 5$ days), and cyclophosphamide ($150 \text{ mg/m}^2/\text{day} \times 5$ days) (Table 1). Treatment was interrupted once due to neutropenic sepsis which was managed with antimicrobial therapy and granulocyte colony-stimulating factor. The tumor regressed to 4-cm diameter.

Consolidation pelvic radiotherapy was administered to 45 Gy followed by two tandem and ovoid implants, bringing the point A dose to 90.2 Gy and the point B dose to 64.1 Gy. She received four additional courses of cisplatin (80 mg/m^2) and

etoposide (400 mg/m^2) administered from April to July 1993, during which time she had no evidence of disease.

All pelvic examinations, Papanicolaou tests, endocervical curettage specimens, and chest roentgenograms have been within normal limits since completion of therapy. She is alive, 5 years after diagnosis, with no evidence of recurrent disease or significant complications of therapy.

DISCUSSION

Sheets and colleagues reported 14 patients with Stage IB or IIA small cell cervical cancer treated either by radical surgery alone or by surgery and postoperative radiotherapy at the University of California, Irvine [2]. Twelve patients were dead of disease within 3 years of diagnosis and the 2 survivors had recurred. Abeler and co-workers reported a 5-year survival rate of 14% among 26 patients with small cell cervical cancer treated at the Norwegian Radium Hospital [3]. Fifteen of these patients had Stage I disease, and of these, 11 had died with disease. These two studies suggest that traditional nonsystemic modes of cervical cancer treatment were not efficacious in the management of small cell tumors.

In light of similar histologic appearances and clinical behavior, Pazdur recommended that the bronchogenic neuroendocrine tumors serve as a model to guide the therapy of endocrine

FIG. 2. Hematoxylin–eosin stained section demonstrating small cell carcinoma of the uterine cervix with hyperchromatic nuclei and scant cytoplasm.

cancers arising from the cervix [4]. He treated three patients with advanced disease with chemotherapeutic agents known to be active in the management of pulmonary oat cell carcinoma. One patient experienced tumor regression in the pelvis and supraclavicular nodal regions of 11 months duration, prior to developing brain metastases. Utilizing a bronchogenic neuroendocrine protocol, Sutton and colleagues documented a partial response of nodal metastases to VAC chemotherapy [5].

The first sustained remission following administration of

VAC chemotherapy was reported by Sheets at the University of California, Irvine [2]. The patient underwent radical hysterectomy, bilateral pelvic and para-aortic lymphadenectomies, and postoperative whole pelvis radiotherapy for a 9-cm diameter exophytic small cell cervical cancer which had metastasized to numerous pelvic and para-aortic lymph nodes. The patient received four courses of VAC chemotherapy and survived without evidence of disease for a minimum of 3 years. O’Hanlan and colleagues have reported an additional two

TABLE 1
Multiagent Intravenous Chemotherapy Regimen and Radiotherapy

Induction ^a	Consolidation	Maintenance ^c
August–December 1992 Cisplatin (80 mg/m ²) Etoposide (400 mg/m ²) <i>Alternating with</i> Vincristine (1.2 mg/m ² /week × 3 weeks) Dactinomycin (300 μg/m ² /day × 5 days) Cyclophosphamide (150 mg/m ² /day × 5 days)	January–March 1993 External beam radiotherapy 4,500 cGy Cesium ¹³⁷ intracavitary implant 2,345 cGy ^b Cesium ¹³⁷ intracavitary implant 2,176 cGy	April–July 1993 Cisplatin (80 mg/m ²) Etoposide (400 mg/m ²)

^a Three courses of cisplatin–etoposide alternating with two courses of VAC.
^b Brachytherapy dosages to left point A.
^c Total of four courses.

TABLE 2
Literature Review—Small Cell Cervical Carcinoma Complicating Pregnancy^a

Author	Age	E.G.A.	FIGO stage	Treatment	Nodes	Status
Turner [10]	26	26 weeks	IB	C/S; RH, PLND adj. chemotherapy	Positive	DOD 9 months, widespread metastases
Kodousek [12]	29	28 weeks	IB	C/S; RH, PLND adj. chemotherapy	Positive	DOD 6 months, widespread metastases
Jacobs [13]	25	10 weeks	IB	Neoadjuvant chemotherapy; RH, PLND radiotherapy	Positive	DOD 24 months, widespread metastases
Lojek [11]	28	25 weeks	IIA	C/S; PLND; radiotherapy adj. chemotherapy ^b	Negative	DOD 32 months, widespread metastases
Chang [14]	27	36 weeks	IB	C/S; RH, PLND radiotherapy	Positive	DOD 2 months, widespread metastases
Perrin [15]	23	25 weeks ^c	IIA	C/S; RH, PLND adj. chemotherapy	Positive ^d	DOD 6 months, widespread metastases
Present	22	30 weeks	IIA	C/S; chemotherapy radiotherapy	Not sampled	NED 5.5 yr

Note. E.G.A., estimated gestational age at diagnosis; C/S, Cesarean section; RH, radical hysterectomy; PLND, pelvic lymphadenectomy; DOD, dead of disease; NED, no evidence of disease.

^a Modified after Turner and colleagues [10]

^b Chemotherapy administered for recurrent disease only

^c Patient presented at 25, 28, 33 & 36 weeks with a cervical mass and vaginal bleeding; actual diagnosis made 6 weeks postpartum

^d Clinically positive; pathological analysis of lymph nodes not stated in manuscript

patients with small cell cervical cancer who have experienced complete responses with systemic therapy lasting 2 to 4 years [6]. Finally, at 21 to 60 months follow-up, Morris and co-workers noted disease-free survival in three patients with Stage IB disease who had received cisplatin, doxorubicin, and etoposide [7].

The model for the induction phase of treatment for our patient was based on protocols used in the treatment of bronchogenic oat cell carcinoma of the lung. Turrise and colleagues demonstrated a 93% complete response rate in patients with small cell lung cancer treated with chemoradiation [8]. Alternating etoposide–cisplatin with VAC was tested in several randomized trials which demonstrated efficacy of this regimen in the treatment of small cell lung cancers [9]. The complete response to chemotherapy and radiotherapy experienced by our patient has subsequently translated into long-term survival.

We were able to find six other case reports of small cell carcinoma of the cervix complicating pregnancy [10–15]. In their clinicopathologic study of 26 patients with small cell cervical cancer, Abeler and colleagues cite a pregnant patient with Stage IB disease who was alive 54 months following definitive surgical treatment and adjunctive chemotherapy [2]. A personal communication from Professor Abeler revealed that this patient did not have a neuroendocrine small cell cervical carcinoma. Rather the patient had the intermediate cell variety of small cell cervical cancer. Thus, we have not included this patient in our review.

Table 2 summarizes the outcomes of the six cases and the current case.

(1) *Pregnancy outcome.* Cesarean delivery was carried out for the five women who were at least 25 weeks pregnant at the time of diagnosis. Five had favorable neonatal outcomes and one neonate who delivered at 26 weeks gestation died of prematurity. The one case diagnosed during the first trimester was treated before fetal maturity could be achieved, resulting in a spontaneous abortion.

(2) *Nodal status.* Four of six patients who underwent pelvic lymphadenectomies had nodal metastases; all four of these patients had Stage IB disease [10, 12–14].

(3) *Survival.* With the exception of the current report, all patients have died of widespread metastatic disease within 3 years of diagnosis of Stage IB ($n = 4$) or Stage IIA ($n = 2$) disease. Four patients survived only 2, 6, and 9 months. These four had been treated initially by radical surgery and either postoperative radiotherapy [14] or adjunctive chemotherapy [10, 12, 15]. The other two patients died 24 and 32 months after diagnosis. One had been treated with a single course of cisplatin preoperatively, followed by radical surgery and postoperative radiotherapy [13], while the other received radiotherapy for a Stage IIA lesion [11].

(4) *Systemic therapy.* Turner and colleagues describe treatment of a Stage IB cervical cancer with a chemotherapy regimen similar to ours [10]. Their patient began systemic treatment 10 days after having undergone radical hysterectomy and pelvic lymph node dissection. Metastatic disease had been found in one hypogastric node. The patient experienced an upper abdominal recurrence and died 9 months after diagnosis.

Although a modest treatment delay to allow fetal maturity for some patients with Stage I *squamous* cell carcinomas of the cervix has not been found to impact negatively on maternal survival [16], such a delay is contraindicated in pregnancies complicated by the *neuroendocrine* cervical cancer. Given the aggressive nature of this tumor type, we advise that therapy be instituted immediately without delay following diagnosis. A viable fetus should be delivered by classical Cesarean section to avoid the lower uterine segment. Induction of systemic therapy followed by radiotherapy should begin in the immediate postpartum period. Patients who insist on treatment delays in order to permit gestational advancement in early pregnancy may be candidates for antepartum systemic therapy and fetal surveillance. Once fetal viability is attained, delivery should be accomplished by Cesarean section with surgical assessment of the para-aortic lymph nodes and debulking of enlarged pelvic lymph nodes. Postoperatively, continued systemic therapy followed by radiotherapy to ports which encompass the extent of disease found on exam and lymph node assessment is required.

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