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CASE REPORT

Adjuvant Therapy for Neuroendocrine Small Cell Carcinoma of the Cervix: Review of the Literature

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Neuroendocrine cell carcinoma of the cervix is a virulent tumor associated with an extremely poor prognosis. Even in clinical Stage I disease, there may be subclinical hematogenous and lymphatic metastases with frequent recurrences. Adjuvant postoperative external pelvic radiotherapy has been reported to offer some degree of local control; however, most patients succumb to distant disease. Following radical abdominal hysterectomy and pelvic lymphadenectomy, with confirmation of the neuroendocrine tumor by electron microscopy and immunohistochemical staining, two patients were given adjuvant systemic chemotherapy with concurrent pelvic radiotherapy, employing regimens with documented activity against small cell carcinoma of the lung of neuroendocrine origin. Despite severe myelotoxicity and persistent neuropathy, both patients are alive without clinical evidence of disease at 28+ and 47+ months.

INTRODUCTION

Small cell carcinoma of the cervix is a rare neoplasm comprising 1–10% of all cervical tumors [1]. It is thought to arise from neuroendocrine cells in the cervix originally derived from embryonic neural crest cells. More than half of the patients with Stage I neuroendocrine cervical tumors have lymph node metastases found at surgery, which contrasts with squamous cell cervical carcinoma, in which the pelvic nodes are involved in about 15% of patients. The majority of the reported cases of early-stage neuroendocrine cervical tumors treated with standard primary therapy consisting of radical hysterectomy and pelvic radiotherapy have died of disease with widespread metastases [2,3]. Adjuvant chemotherapy has been suggested; however, due to the rarity of this tumor, no optimal regimen has been delineated [4–6].

Two cases of neuroendocrine small cell carcinoma of the cervix treated with adjuvant chemo- and radiotherapy at the Jack D. Weiler Hospital of the Albert Einstein College of Medicine, Montefiore Medical Center, New York, are reported.

CASE 1

R.R. is a 62-year-old woman who presented with postmenopausal bleeding and underwent biopsy of a 2-cm exophytic lesion on the posterior aspect of the cervix. The light microscopic appearance was consistent with a small cell carcinoma. Metastatic workup, including CT of the chest, abdomen, and pelvis, flexible sigmoidoscopy, and cytoscopy failed to reveal evidence of metastatic disease. The patient underwent examination under anesthesia, exploratory laparotomy, radical abdominal hysterectomy with bilateral salpingo-oophorectomy, and radical pelvic and low para-aortic lymphadenectomy.

On light microscopy, the tumor was composed of small, round to spindle-shaped cells with finely stippled chromatin and scant indistinct cytoplasm, forming nests and sheets that infiltrated approximately 50% of the cervical wall. Focal necrosis, crush artifact, and a high mitotic rate were apparent (Fig. 1). The tumor arose at the transition zone. The infiltrative border was rounded, relatively well circumscribed, and associated with a moderate lymphocytic host response. Immunocytochemistry disclosed positive staining for chromagranin and Leu-7, compatible with neuroendocrine histogenesis [7,8]. Electron microscopy revealed rare neurosecretory granules (Figs. 2 and 3). There was no evidence of lymphovascular invasion, and none of the 32 lymph nodes contained tumor.

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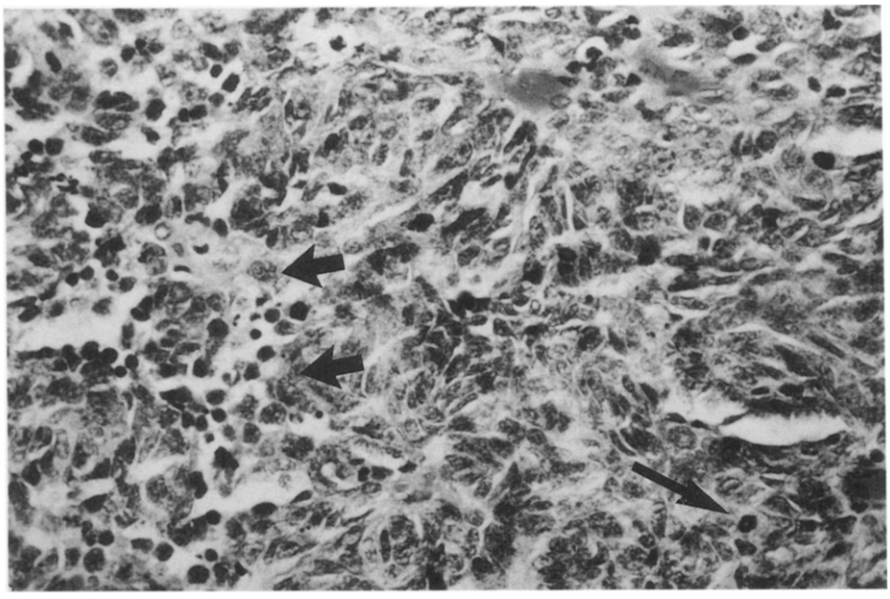

FIG. 1. Case 1: Tumor cells are round to spindle-shaped with scant cytoplasm and delicate chromatic. Mitoses are evident (single arrow) as well as individual cell necrosis (double arrow) (H&E, ×310).

Postoperatively, the patient underwent further metastatic workup including a CT scan of the brain, bone marrow biopsy, and bone scan, all of which were negative. She received adjuvant chemotherapy consisting of five courses of cyclophosphamide (500 mg/m^2) on Day 1, with 3 days of etoposide (80 mg/m^2) and cisplatin (33 mg/m^2) [9]. The dose of cyclophosphamide was increased to 1000 mg/m^2 by the third course of chemotherapy and subsequently decreased for the last two courses when nadir white blood cell counts fell below 1000/dl. The dose of etoposide was decreased to 60 mg/m^2 daily for 3 days on the fifth course. The cisplatin dose was not changed. The total doses of chemotherapy were 500 mg/m^2 cisplatin, 1140 mg/m^2 etoposide, and 3730 mg/m^2 cyclophosphamide. External pelvic radiotherapy commenced during the fourth course of chemotherapy. The patient received a total of 46 Gy in 99 elapsed days.

Complications from this combination therapy included one NCI grade 3 (500–999/mcl) and three grade 4 leukocyte nadirs (<500/mcl) and two grade 4 platelet nadirs

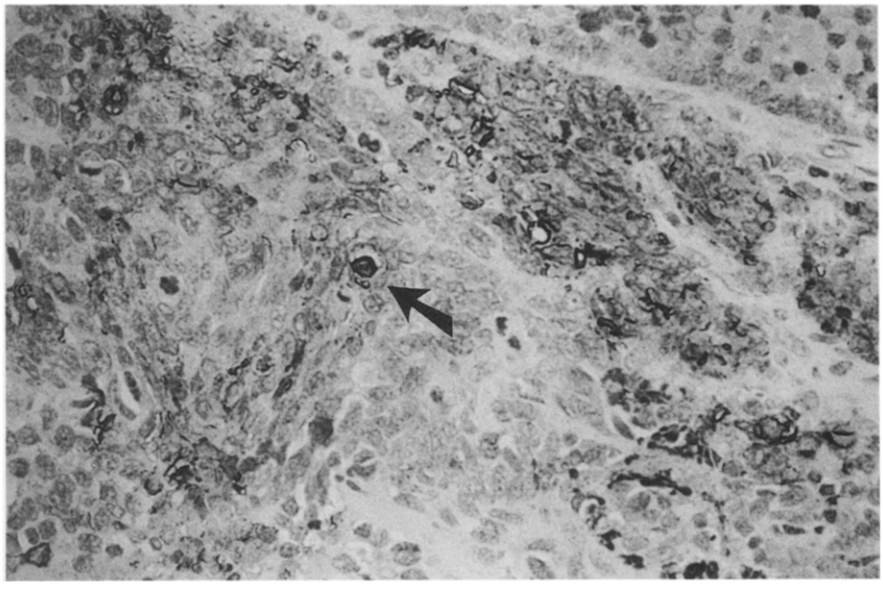

FIG. 2. Case 1: Immunoperoxidase staining for Leu 7, a neuroendocrine marker, is positive in many of the cells (hematoxylin counterstain, ×310).

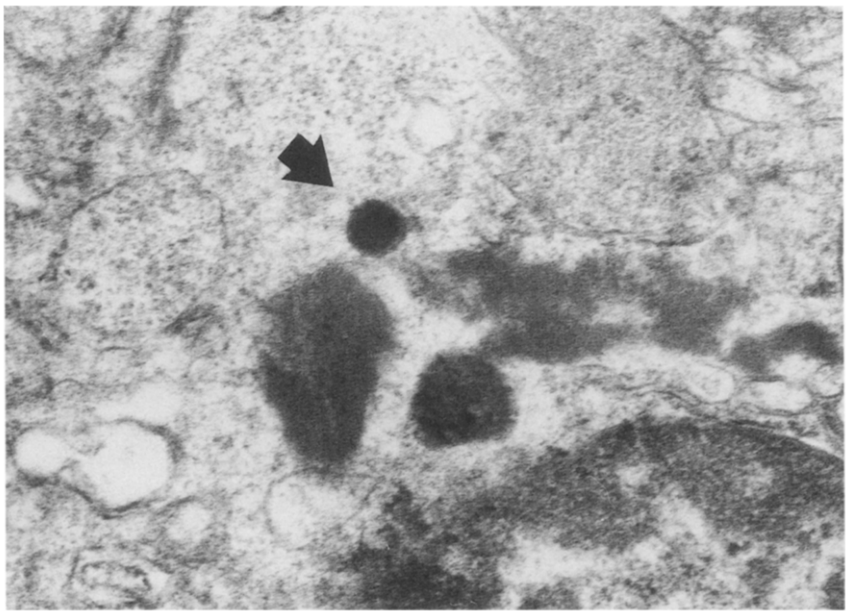

FIG. 3. Case 1: Rare neurosecretory granules were identified on electron microscopy (Original magnification, ×36,000).

(<25,000/mcl), necessitating two admissions during which 9 units of packed red cells and five 6-unit transfusions of platelets were administered. Ten months after completion of the therapy, the patient was admitted with a partial small bowel obstruction. A metastatic workup was negative, and the obstruction resolved with nasogastric suction. She was again admitted at 17 months post-therapy for a transient partial small bowel obstruction. At 47+ months, the patient is alive without evidence of disease. She has a persistent grade 3 sensory peripheral neuropathy, but this has ameliorated somewhat over the ensuing years.

CASE 2

B.H. is a 41-year-old female who underwent biopsy of an exophytic tumor on the anterior lip of the cervix. The initial diagnostic interpretation of the biopsy material was poorly differentiated small cell carcinoma. By clinical staging, including a negative cystoscopy and sigmoidoscopy, the patient had Stage IB disease. The patient underwent examination under anesthesia with exploratory laparotomy, radical pelvic and low para-aortic lymphadenectomy, radical abdominal hysterectomy with bilateral salpingo-oophorectomy, and appendectomy. Extensive histologic sampling revealed a small cell neoplasm. The cells were round to spindle-shaped, containing fine chromatin, with a high mitotic rate, and multiple foci of necrosis and crush artifact. Additionally, the tumor demonstrated the focal presence of rosettes (Fig. 4). The tumor arose at the squamocolumnar junction and infiltrated as loosely cohesive nests and sheets through 1/3 of the thickness of the cervical wall. The deep margin of involvement was well demarcated and associated with a moderate host response. Stains for Leu-7, synaptophysin, neuron-specific enolase, and chromogranin were all focally positive, consistent with small cell carcinoma of neuroendocrine origin (Fig. 5). Electron microscopy on paraffin-embedded material was noncontributory. A single focus of lymphatic permeation was found adjacent to the tumor, but there was no evidence of metastatic tumor in any of the 25 lymph nodes received.

Adjuvant chemotherapy consisted of etoposide (200 mg/m^2) and cisplatin (100 mg/m^2), administered over 5 days starting 3 weeks postoperatively for a total of five courses. External pelvic radiotherapy commenced with the first course of chemotherapy [8,9]. Doses of etoposide were decreased according to nadir white blood cell counts. The total doses of chemotherapy were 475 mg/m^2 cisplatin and 520 mg/m^2 etoposide. A total of 45 Gy was administered over 39 elapsed days. The patient experienced one NCI grade 1 (1500–1999/mcl), one grade 2 (1000–1499/mcl), and one grade 4 (<500/mcl) episodes of granulocyte toxicity, requiring one hospital admission. The patient developed a grade 3 neurosensory toxicity that has ameliorated minimally since cessation of therapy. She remains clinically without evidence of recurrent disease at 28 months.

DISCUSSION

The aggressive nature of the neuroendocrine-derived small cell carcinoma has been most clearly described by Sheets *et al.* [3], who detailed the clinical histories of 14 Stage IB or IIA patients, with 13 undergoing radical surgery. Twelve of these patients were dead of disease 8–

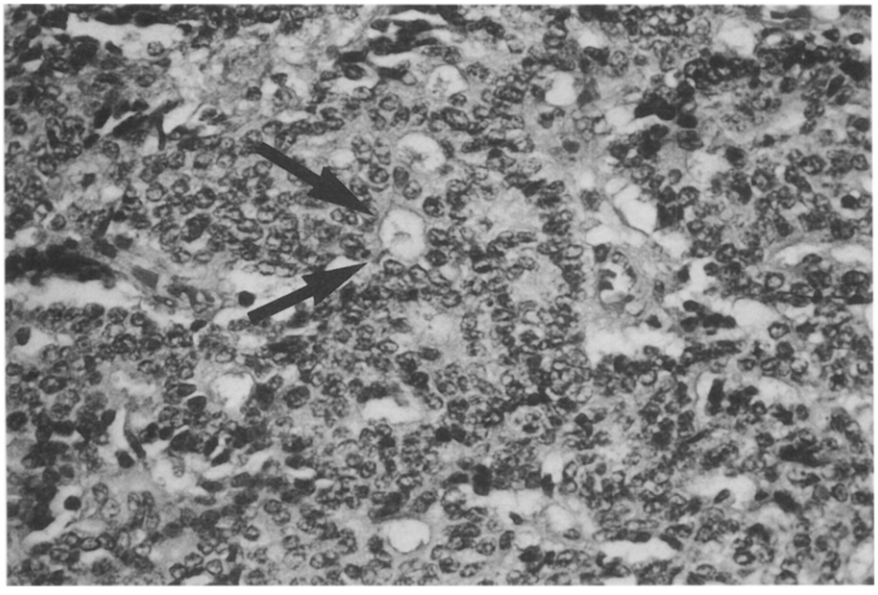

FIG. 4. Case 2: In this small cell carcinoma, occasional rosettes are present (H&E, ×310).

31 months after treatment, and two were being treated for recurrence. The tendency of this tumor to disseminate via hematogenous and lymphatic routes [4–6] emphasizes the need for systemic therapy. Jacobs *et al.* [9] reported the administration of one course of neoadjuvant cisplatin (50 mg/m^2) to a pregnant patient with a 3-cm cervical lesion, without evidence of a response. After radical hysterectomy, the patient received pelvic radiotherapy, but subsequently expired [10]. Pazdur and colleagues were the first to recommend that neuroendocrine cervical tumors be treated similarly to neuroendocrine tumors of the lung given their similar histologic appearance and pathologic behavior [11]. They treated a patient with chemotherapy, obtaining a short-term complete response. In 1986, Turner and colleagues administered adjuvant postoperative vincristine, Adriamycin, cyclophosphamide, etoposide, and cisplatin to a patient with Stage IB neuroendocrine cervical carcinoma with a single metastasis to the left hypogastric node [4]. This patient developed disease recurrence in the liver and bone marrow and died 10 weeks after cessation of chemotherapy. Siedel and Steinfeld reported the administration of 5-fluorouracil

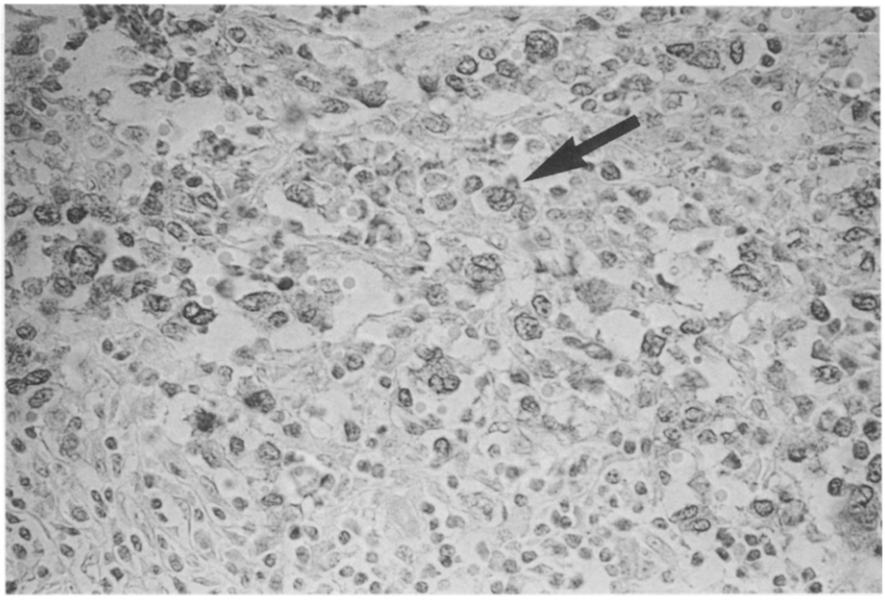

FIG. 5. Case 2: Immunoperoxidase staining for neuron-specific enolase is positive in many tumor cells (hematoxylin counterstain, ×310).

with streptozotocin and, later, Adriamycin to a patient with neuroendocrine cervical carcinoma recurrent in the lung 4 years after radical surgery [6]. The patient died with brain metastasis 1 month after initiation of therapy. In 1988, Sutton *et al.* reported a partial response to vincristine, Adriamycin, cyclophosphamide (VAC) chemotherapy for primary cervical neuroendocrine tumor recurrent in the mediastinum [12]. Sheets *et al.* have also reported administering adjuvant VAC chemotherapy after surgery and radiation to a patient with primary neuroendocrine cervical carcinoma within the pelvis who has remained without evidence of disease for 36 months [3].

At the time of presentation of each of our patients, a review of the reported chemotherapy regimens for neuroendocrine carcinoma of the lung was undertaken. Kwiatkowski and colleagues [13] reported that 94% of evaluable patients with small cell carcinoma of the lung had responded to a regimen of cyclophosphamide, etoposide, and cisplatin, given at 3-week intervals, with a planned eight courses. After 400 mg/m^2 of cisplatin had been administered they substituted Adriamycin. Radiation therapy was administered during cycles 4 and 5 of chemotherapy. Much of the latest chemotherapeutic investigation of small cell lung carcinomas has focused on etoposide and cisplatin, with concurrent radiotherapy [14,15]. Turrisi *et al.* reported a 93% complete response rate in their patients with small cell lung cancer treated with combination chemoradiotherapy [14]. Since pelvic portals of radiotherapy encase a greater volume of marrow than mediastinal portals, it was expected that these regimens would be much more myelotoxic than reported. Complete blood counts were obtained weekly after an informed consent was signed for each chemoradiation protocol. Despite severe myelotoxicity during therapy, the long-term sequelae of both protocols consisted only of neuropathy. As with small cell carcinoma of the lung, complete responses to chemotherapy and radiotherapy has gradually translated into prolonged survival and occasional cure. Prompt postoperative initiation of chemotherapy may play an important role with respect to obtaining maximal survival, as this tumor histotype may undergo transition over time into a more malignant, less-differentiated cell type [16]. This highlights the theoretical importance of eradicating the more susceptible cell clones early in the course of the disease and supports the use of primary adjuvant therapy. On the basis of these two patients and a review of the literature, we suggest that chemotherapy with concurrent pelvic radiation therapy be administered in the adjuvant setting after appropriate radical surgery. This may increase patient survival and possibly cure some patients with early clinical stage neuroendocrine cell carcinoma of the cervix, despite the tendency for early distant metastasis. In view of the fact that these tumors are so rare, multicenter, randomized, controlled trials would be necessary to confirm this observation.

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